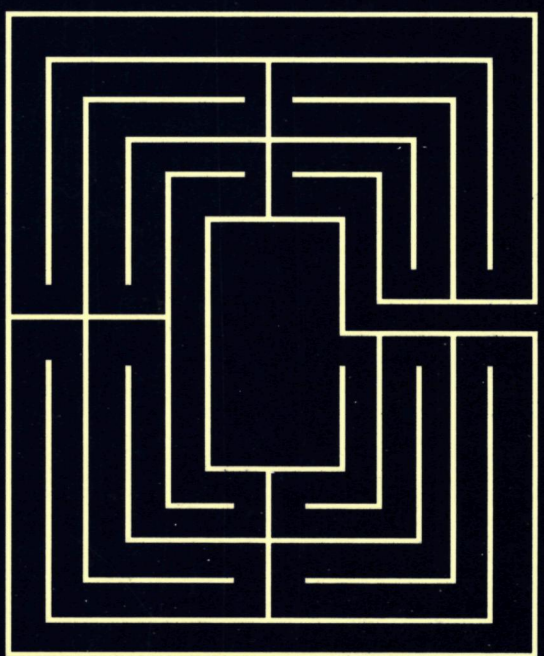
Catalyst Systems for the Epoxidation of Alkenes by Molecular Oxygen



Patricia Ann Gosling

Catalyst Systems for the Epoxidation of Alkenes by Molecular Oxygen

Een wetenschappelijke proeve op het gebied van de Natuurwetenschappen

Proefschrift
ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen in het openbaar te verdedigen
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PATRICIA ANN GOSLING
geboren op 14 juni 1963 te Stamford, Connecticut (U.S.A.)

Promotor: Prof. Dr. R.J.M. Nolte

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Do I dare
Disturb the universe?
In a minute there is time
For decisions and revisions which a minute will reverse

For I have known them all already, known them all
Have known the evenings, mornings, afternoons,
I have measured out my life in coffee spoons,
I know the voices dying with a dying fall
Beneath the music from a farther room
So how should I presume?

--T S Eliot, 1917

Labor is blossoming or dancing where
The body is not bruised to pleasure soul,
Nor beauty born out of its own despair,
Nor blear-eyed wisdom out of midnight oil
O chestnut-tree, great-rooted blossomer,
Are you the leaf, the blossom or the bole?
O body swayed to music, O brightening glance,
How can we know the dancer from the dance?

--W B Yeats, 1927

Acknowledgment

This thesis would never have been written without the assistance and support of many people at the University of Nijmegen and beyond

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The work in this thesis was carried out in conjunction with the goals of the IOP-Catalysis Program and I would like to thank the members of my supervisory committee, Dr Hans de Vries, Dr Michael Doyle, and Prof Dr Richard Kellogg for their enthusiasm and useful suggestions for carrying out this reasearch project

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Patricia

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Chapter 1

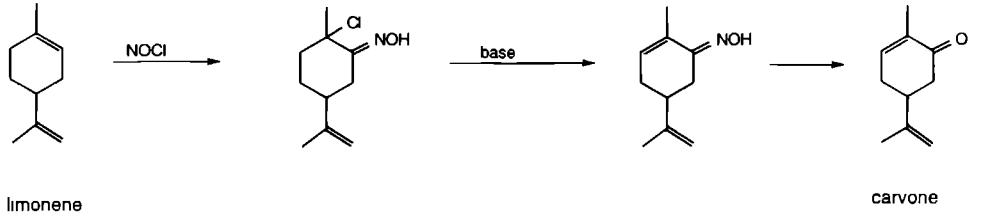
General Introduction

The oxidation of organic compounds is important in both industrial and laboratory-scale chemical processes The epoxidation of alkenes, in particular, provides a valuable means of introducing a reactive functional group into a hydrocarbon Epoxides are more reactive than normal ethers due to the strain in the three-membered oxirane ring and the electron density on the oxygen atom Nucleophilic attack on one of the carbon atoms of the epoxide ring can create ol variety of new compounds including diols, β-hydroxy ethers, ethanolamines, and halohydrins In addition to these products, epoxides can be converted to ketones, aldehydes, allylic alcohols, alcohols and polyethers Because of this versatility, epoxides are important synthetic intermediates In addition, asymmetric attack of the double bond is a means of introducing a chiral center into a prochiral substrate The need to produce enantiomerically pure pharmaceuticals has fueled the drive for developing catalysts capable of producing chiral epoxides [1]

In recent years, the effort to develop more efficient means of epoxidizing alkenes has been concentrated in the area of catalysis Much work has been done in developing new transition metal complexes to catalyze the epoxidation of alkenes by a variety of oxidants including sodium hypochlorite, hydrogen peroxide, and iodosylbenzene There is also increasing interest in the use of molecular oxygen as the terminal oxidant in these reactions Because we have a continual supply in the air around us, molecular oxygen is an inexpensive and environmentally-compatible oxidant The use of molecular oxygen is not only of interest for large scale industrial preparations, we can also gain valuable insight into the nature of the metal-oxygen interaction that occurs with some enzymes and enzyme mimics

Within the framework of the IOP-Catalysis Program the work in this thesis was carried out with the goal of developing epoxidation catalyst systems using molecular oxygen that are viable for industrial scale processes The most recent successes in the area of epoxidation catalysis have been with the chiral catalysts designed by Sharpless[2] and Jacobsen[3] which are being used to produce good yields of chiral epoxides with high enantioselectivities on a limited industrial scale, although not with molecular oxygen as oxidant

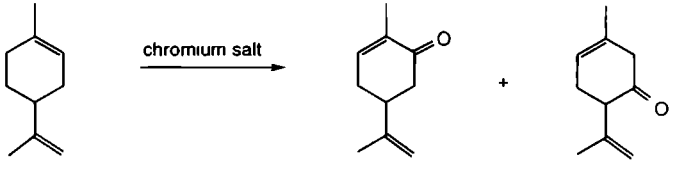
It has recently become of interest to synthesize greater quantities of carvone Carvone is an important component of the flavor and fragrances industry and much of it is isolated from natural materials The remainder is produced synthetically on a 1000-1500 ton scale The current synthetic production of carvone involves the use of limonene as a starting material and nitrosylchloride as a reagent (Scheme 1 1) [4] This process has adverse consequences for the environment and is therefore considered an unattractive route for the synthesis of carvone



limonene carvone

Scheme 1.1

As an alternative route, carvone is available by means of the oxidation of limonene with chromium catalysts [5] The yield from this process, however, is low (36%) and isopiperitenone is formed as a byproduct in a yield of 31% (Scheme 1 2)



isopiperitenone

Scheme 1.2

A more attractive route would be one in which molecular oxygen is used as the oxidant From some of the work described in this thesis, such a route is feasible using nickel catalysts for the epoxidation of limonene as the first step in the reaction sequence

Outline of the thesis

Our investigations in the area of homogeneous catalysis for the epoxidation of alkenes by molecular oxygen are described Two approaches were developed to explore the possibilities of using molecular oxygen as the terminal oxidant in epoxidation reactions One approach involved the use of a manganese(III) porphyrin in conjunction with a rhodium(III) bipyridine complex and formate for the reductive activation of molecular oxygen The second approach used molecular oxygen as the oxidant in conjunction with nickel(II) complexes and an aldehyde
Chapter 2 provides background material and an introduction to some of the recent work that has been done in the area of epoxidation of alkenes by transition metal catalysts, including studies on porphyrins as agents in the reductive activation of molecular oxygen and the special challenges presented in using molecular oxygen as an oxidant

Chapter 3 describes a manganese(III) porphyrin/Rh(III)bipyCp*Cl/formate catalyst system for the epoxidation of alkenes in a two-phase (organic/aqueous) system
In Chapter 4 an adaptation of the above-mentioned manganese(III)/rhodium(III) catalyst couple, in which the two metal groups are linked *via* a π-conjugated bridge, is described, including the nature of the reduction of manganese(III) to manganese(II) by the rhodium(III) / formate couple, and the activity of these complexes as catalysts
Chapter 5 describes a second approach for the use of molecular oxygen as oxidant in a system with nickel(II) β-diketonate complexes as catalysts in conjunction with an aldehyde The scope and utility of this reaction are described
In Chapter 6 the results of a kinetic study of the nickel(II) β-diketonate/aldehyde/O_2 catalyst system are summarized and a mechanism for the reaction is proposed
Chapter 7 expands on the use of nickel(II) complexes as catalysts by describing nickel(II) oxamide and indole complexes and their utility as catalysts under similar reaction conditions as those described in Chapter 5
Finally, in Chapter 8 the results of functionalizing a catalyst center with a cavity-containing binding site are presented Nickel(II) and manganese(III) salophen complexes functionalized with molecular clips, and their potential use in the selective epoxidation of alkenes, are described

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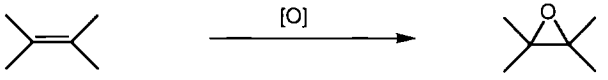
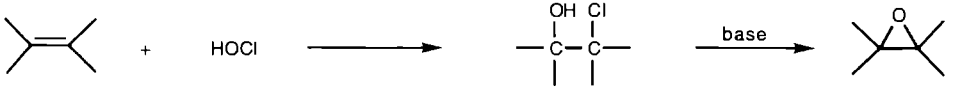
Literature Survey

2.1 Epoxides

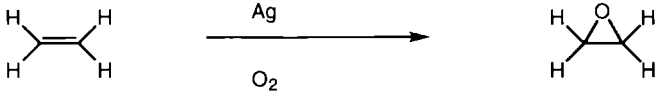
Epoxides (also called oxiranes) are three-membered cyclic ethers which--compared to other ethers--show relatively high reactivity due to the electron density on the oxygen atom and the strain in the three-membered ring. Epoxides are usually prepared from alkenes in a reaction that formally involves the insertion of an oxygen atom into the double bond of the alkene.[1]



Historically, epoxides have been prepared by several different methods. The first industrial process, called the chlorohydrin process, was developed in 1859-60 for the epoxidation of ethene and propene.[2] This process involves the attack on the alkene by *in situ* prepared hypochlorous acid The chlorohydrin that is formed is treated with base to form the epoxide and the corresponding chloride salt.

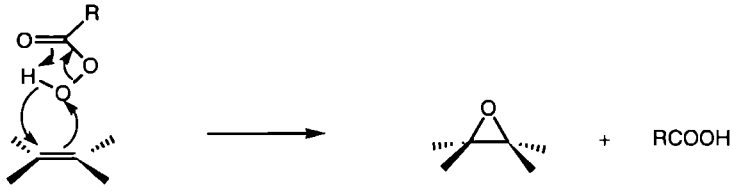


For the preparation of ethene oxide, the halohydrin process has been replaced by direct epoxidation using oxygen in conjunction with a silver catalyst. This reaction was developed in 1931 and is a highly successful industrial process. A major drawback of this reaction is that only ethene can be epoxidized under these reaction conditions Other alkenes are mainly oxidized to water and carbon dioxide.

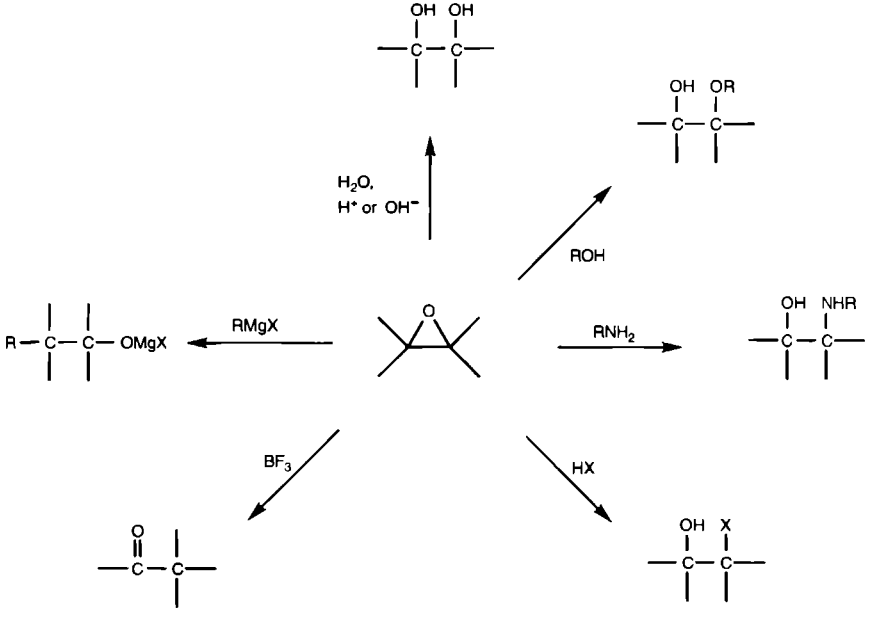


Another widely used route for the epoxidation of alkenes, particularly on a laboratory scale, is the use of peroxy acids as epoxidizing agents.[4] Peroxy acids react directly with alkenes to form epoxides in good yields without the need for a catalyst. Peroxy acids, however, are difficult to

handle and large scale operations are dangerous because of the potentially explosive nature of these reagents

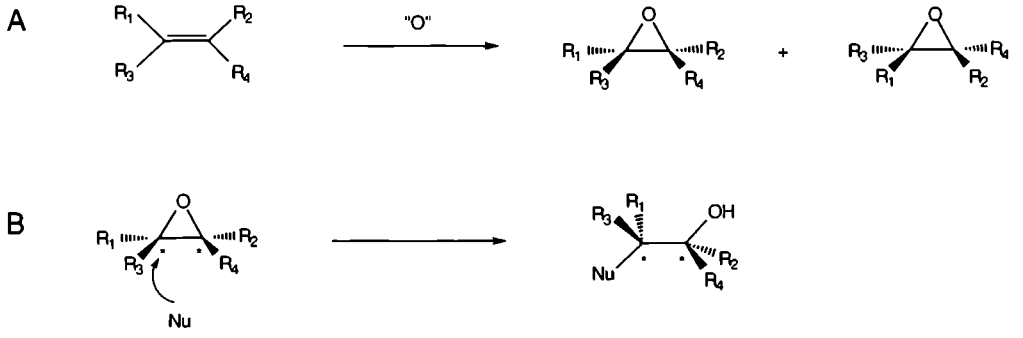


Epoxides are useful synthetic intermediates because of the wide range of reactions they can undergo to form a variety of functionalized compounds [5] Some of the transformations that an epoxide can undergo are depicted in Scheme 2.1



Scheme 2.1

In addition to the reactions depicted in Scheme 2 1 , prochiral alkenes provide an excellent means of building chirality in the carbon skeleton of compounds that are important in the pharmaceutical and agro-chemical industries [6] The epoxidation of a prochiral alkene to an epoxide and subsequent reaction with a nucleophile, affords the opportunity of building one or two chiral centers into the molecule (Scheme 2 2)



Scheme 2.2 *Synthesis of chiral epoxides from a prochiral alkene (A). Nucleophilic addition to epoxide to give a compound with two chiral centers (B).*

2.2 Epoxidation with Transition Metal Catalysts

A number of epoxidation routes have been developed in recent years which involve the use of soluble transition metal catalysts for the catalytic epoxidation of alkenes in the presence of an appropriate oxidant.[7] Many of these catalysts contain a square planar (sometimes macrocyclic) ligand system and any of a number of transition metals, most importantly, Mn, Fe, Co, Ni, and more recently Ru.[7c] The intense interest in developing soluble transition metal catalysts for the epoxidation of alkenes has grown in recent years as a result of the need for more efficient, safer, and more environmentally compatible epoxidation processes. Soluble transition metal catalysts that can be used in a homogenous reaction system in conjunction with an oxygen atom donor have the potential of providing greater selectivity in terms of reaction products formed and fewer by-products, leading to less waste. Other reasons for the development of transition metal catalysts for the homogeneous epoxidation of alkenes are summarized as follows:

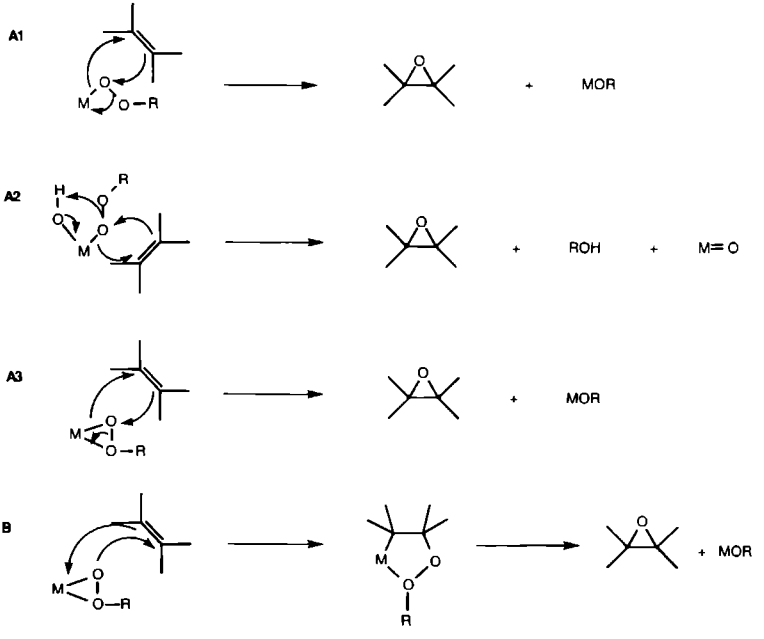
- investigations into metal catalyzed oxidations can give greater insight into biochemically important reactions such as oxidations by monooxygenases, oxygen binding, and transport.
- transition metal catalysts in solution afford better control over oxidation products formed than do hetergeneous catalysts, and are useful for carrying out partial selective oxidation.
- the need has grown to develop more efficient methods of functionalizing the lower alkenes that are by-products of the petroleum cracking industry
- the growing interest in the use of chiral epoxides as synthons in the pharmaceutical and agro-chemicals industries provides an incentive for the development of enantioselective catalysts

To date, several researchers have studied the potential of a wide variety of transition metals coordinated to different ligand types in conjunction with a range of oxygen atom donors such as

hypochlorite ion, iodosylbenzene, alkylperoxides, hydrogen peroxide, and molecular oxygen [7a 7b 8] Molecular oxygen forms a special case and will be discussed in detail in Section 2 3 2 On the basis of the reactive intermediate responsible for oxygen transfer to the alkene, transition metal epoxidation catalysts can be divided into three broad categories

1 Transition metal peroxide / peroxo complexes
2 Transition metal-oxo complexes
3 Peroxo radicals

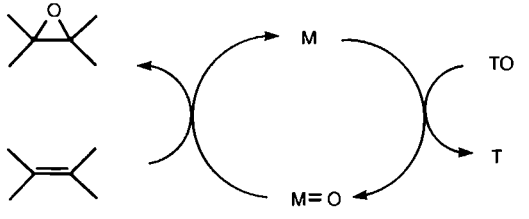
Transition metals in groups IV, V, and VI of the periodic table with the exception of chromium belong to the first category Complexes of titanium, vanadium, molybdenum, and tungsten, in particular, are very good epoxidation catalysts in combination with alkyl peroxides or hydrogen peroxide These metals have a low redox potential, are labile with respect to ligand substitution and are all Lewis acids in the highest oxidation state, d^0, whereby coordination of a peroxide/peroxo group is possible in order to activate the peroxide for nucleophilic attack of the alkene The active oxidizing species contains a mono- or bidentate coordinated alkyl or hydrogen peroxide of a coordinated peroxo group Oxygen transfer from the active metal oxygen complex to the alkene can occur *via* two general mechanisms (A and B in Scheme 2 3)[9 1c]



Scheme 2.3 *The mechanism of oxygen transfer from a metal-peroxide to an alkene via a nucleophilic attack from the alkene on the monodentate (A1, A2) or bidentate (A3) coordinated alkylperoxide group The mechanism involving a peroxometal ring (B)*

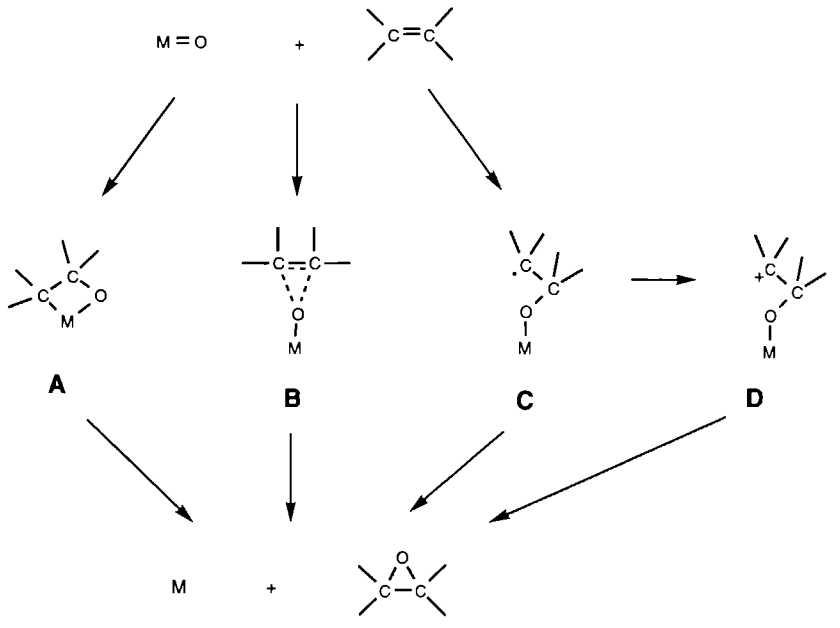
The transition metals in groups VII - IX, including chromium, belong to the second category of transition metal epoxide catalysts In addition to alkyl peroxides, hydrogen peroxide and molecular oxygen, this group of metals can utilize iodosyl compounds, hypochlorite, and N oxides as oxygen atom donors for the formation of a catalytically active oxidant [10]

Epoxidation with these catalysts proceeds *via* an "oxygen-rebound" mechanism as suggested by Groves[11] (Scheme 2 4) The catalytically active oxidizing species is a reactive metal-oxo complex (M=O) This mechanism requires the metal atom to act as a relay for the oxygen transfer of the terminal oxidant (the oxygen atom donor) to the alkene *via* this metal-oxo complex The alternation of the metal complex between these two states corresponds formally to an oxidative-addition / reductive-elimination sequence Therefore, metals that can easily undergo two-electron changes such as Fe(III), Mn(III), Cr(III) and Ru(IV) are effective catalysts



Scheme 2.4 *"Oxygen-rebound" mechanism (TO is the terminal oxidant)*

The transition metals in the second category have partially filled d-orbitals that can be affected by the structural and electronic changes around the metal atom [12,7a] Therefore, different electronic states of the metal-oxo complex are possible Changes in the nature of the ligand coordinated to the metal can have an effect on the mechanism of the oxygen transfer from the metal-oxo species to the alkene Oxygen transfer can occur through various intermediates which can be divided into two classes A number of these possibilities is shown in Scheme 2 5 In the first class the oxygen transfer occurs through the interaction of the alkene with the oxygen atom that is bound to the metal center (Scheme 2 5 B-D) In the second class a metallo-ring is formed through the interaction of the alkene with the oxygen atom of the metal (Scheme 2 5 A)



Scheme 2.5 *Possible intermediates in the oxygen transfer step between an oxo metal complex and an alkene*

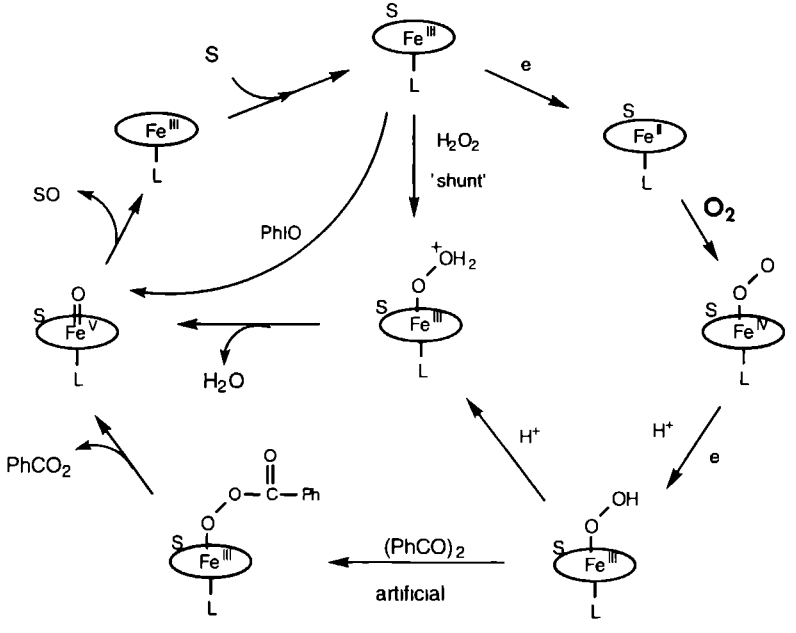
The third category of transition metal epoxidation catalysts comprises metals that can initiate the formation of peroxo radicals These metals often belong to group VI IX and the peroxo radicals are usually formed with metals that can easily undergo a one electron transfer process such as Mn(II), Fe(II) and Co(II) Epoxidation occurs of those alkenes where abstraction of an allylic hydrogen atom is less favorable than oxygen addition to the double bond Many cobalt(II) complexes catalyze epoxidations *via* this radical mechanism [13] Valentine and co-workers have shown that even simple metal salts of manganese, iron, copper and cobalt are capable of epoxidizing alkenes in the presence of iodosylbenzene [14] Zinc, nickel and silver salts are inactive as catalysts under these conditions For these epoxidations, an alternative mechanism has been suggested whereby the oxidation state of the metal ion is not changed and an electrophilic attack of iodine occurs on the alkene

In an attempt to give a brief overview of the most recent work that is relevant to this thesis, some of the more important types of epoxidation catalysts will be discussed in the following section Porphyrins, the most intensely studied transition metal catalysts with macrocyclic ligands will be discussed first [15a] In recent years however, other more easily modified square planar complexes, designed to mimic the catalytic potency of the porphyrins have received a great deal of attention

2.2.1 Metallo-porphyrins

In 1979, Groves and co-workers published a report that described the use of Fe(III) tetraphenylporphyrin (FeTPP) as an epoxidation catalyst using iodosylbenzene as oxidant [15b] This work was the result of attempts to mimic the action of a monooxygenase, cytochrome P-450 which, as an enzyme, is able to activate molecular oxygen for the purpose of monooxygenase reactions including the epoxidation of alkenes The publication of this work opened up a new field in biomimetic chemistry, but, perhaps more importantly, it created a new focus in the field of oxidation catalysis

The success of this work, and earlier work by Hrycay,[16] created the notion of the "peroxide shunt" and the "short path," which bypass the need for a reducing agent in the reductive activation of dioxygen by metallo-porphyrins (Scheme 2 6) Reproduction of the reductive activation of dioxygen in the laboratory is tedious due to the many steps involved and investigators could, by making use of the peroxide shunt, directly study the nature of the metal-oxygen bond, or carry out catalytic oxidations with high yields of products using such oxygen atom donors as iodosylbenzene, hypochlorite ion, and hydrogen and alkyl peroxides [8u 15,17]

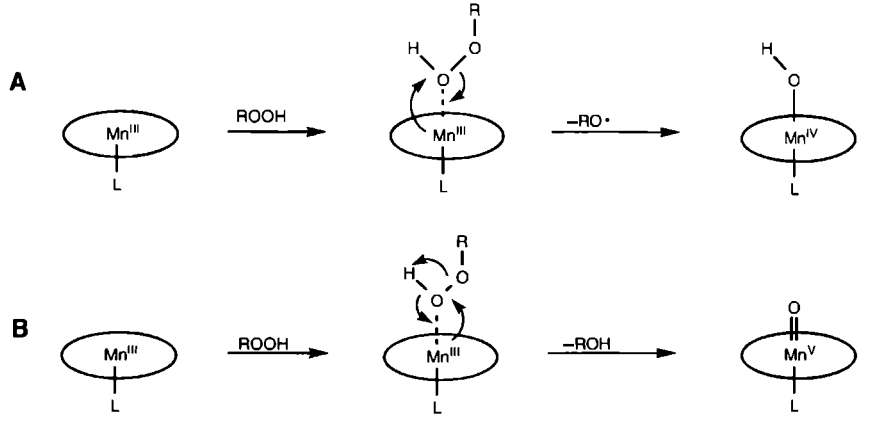


Scheme 2.6 Catalytic cycle of cytochrome P-450 S = substrate, L = ligand

The crucial step in the epoxidation sequence avoided by the use of the peroxide shunt is the reduction of the Fe(III) porphyrin to the +2 oxidation state This reduction must occur for oxygen to be able to bind to the metal center Use of single oxygen atom donors eliminated the need for a source of electrons for the reduction steps

The investigation into this type of epoxidation quickly intensified and several transition metals and a variety of porphyrin ligands were studied to determine the scope of using metalloporphyrins as catalysts in epoxidation reactions. The most successful and the most widely studied of the porphyrin-type catalysts are based on Mn(III).[7b] Porphyrins were used as ligands in these reactions because the highly stable aromatic system stabilized the different oxidation states of the mangenese ion and provided a means of studying biologically relevant manganese and iron enzyme systems. Several oxygen atom donors can be used in conjunction with manganese(III) porphyrins to achieve the epoxidation of alkenes, including iodosylbenzene, sodium hypochlorite, alkyl peroxides and hydroperoxides, as well molecular oxygen in conjunction with an electron source. With iodosylbenzene as oxygen atom donor, Mn(III)TPP catalyzes the epoxidation of alkenes by first forming an unstable and reactive oxo-MnTPP complex which then epoxidizes the alkene. The oxygen transfer process takes place in a nonstereospecific manner. Epoxidation of *cis*-stilbene gives both *cis*- and *trans*-stilbene oxide in the ratio of 35:65.[17c]

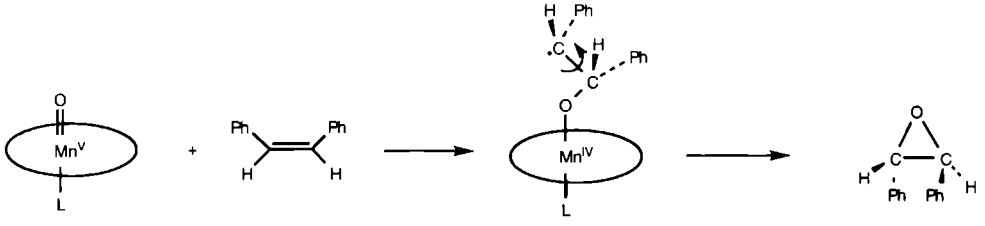
Hypochlorite ion is another frequently used source of oxygen atoms for manganese porphyrin catalyzed epoxidations.[8u,18,17d] Used alone, the combination of hypochlorite ion and Mn(III)TPP is a poor epoxidizing system, but the presence of pyridine or *N*-methylimidazole in the reaction solution significantly improves epoxide yields.[8u,19] These nitrogen bases act as axial ligands that coordinate to the manganese center of the porphyrin molecule and stabilize the manganese-oxo complex. The presence of a small amount of a nitrogen base increased the rate of the reaction, the selectivity for epoxidation, and affects the stereoselectivity. In the absence of pyridine the *cis/trans* ratio for the epoxidation of *cis*-stilbene was 35·65. In the presence of pyridine, a ratio of up to 94·6 had been found.[8u] Hydrogen peroxide and alkyl peroxides can also be used as oxygen atom donors in epoxidation reactions catalyzed by manganese porphyrins.[20] The major drawback of these oxidants being that homolytic cleavage of the peroxide is predominant, leading to the formation of a radical The homolytic oxidation, involving a one-electron transfer and the heterolytic oxidation, involving a two-electron transfer process that occurs in the manganese porphyrin/peroxide system are shown in Scheme 2.7.



Scheme 2.7 *One-electron oxidation (A), and two-electron oxidation (B) with alkyl and hydrogen peroxide and Mn(III) porphyrin.*

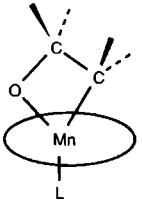
Without imidazole in the reaction system only traces of epoxide are formed when alkyl peroxides are used as the oxygen atom donor [20a] In the presence of imidazole, however, epoxide yields approach those achieved with iodosylbenzene as the terminal oxidant

Alkenes tend to show varying reactivites in Mn(III) porphyrin catalyzed epoxidations with electron rich alkenes reacting faster than electron-poor alkenes [7b 17d] The loss of stereochemistry in the epoxidation of alkenes catalyzed by Mn(III) porphyrins can be explained by the formation of a radical intermediate during the oxygen transfer process This intermediate would have to have a life-time long enough to allow for isomerization (rotation around the carbon carbon bond) to occur (Scheme 2 8)



Scheme 2.8 *Loss of stereochemistry in the epoxidation of cis-stilbene by an oxo manganese(V) porphyrin complex*

Conflicting views still exist about the presence of a radical species in the reaction pathway and about the existence of an oxo-manganese porphyrin alkene species with radical character [8n 8r] For example, a metallacyclic intermediate, called a metallaoxetane (**1**), has also been suggested that forms during oxygen atom transfer to the alkene [8r] The most recent mechanistic studies reported by Bruice and co-workers[21] reject the possibility of a metallaoxetane, a π-radical cation, a carbocation, and a carbon radical as intermediates in oxygen atom transfer Instead they suggest that the mechanism of oxygen atom transfer is concerted, leading to conservation of stereochemistry, and that other products formed during the epoxidation reaction are a result of competing parallel side reactions

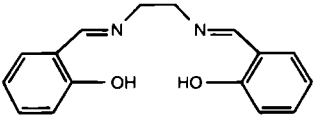


1

As the exact nature of the transition state of the oxygen transfer is still a matter of controversy, this area of investigation remains very active with new insights continually appearing in the literature.

2.2.2 Metallo-salen and related catalysts

The success of using metallo-porphyrins, in particular Mn(III) porphyrins, as epoxidation catalysts with a variety of oxygen atom donors naturally led to the search for other active transition metals coordinated to non-porphyrin ligands The salen ligand **2** was a natural choice as an alternative ligand, because it is square planar and extremely easy to prepare from salicylaldeyde and ethylene diamine Salen type ligands are also easily modified by the judicious choice of a salicylaldehyde derivative and the appropriate diamine



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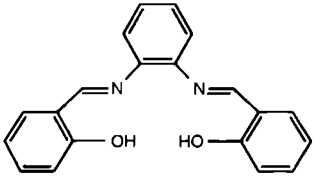


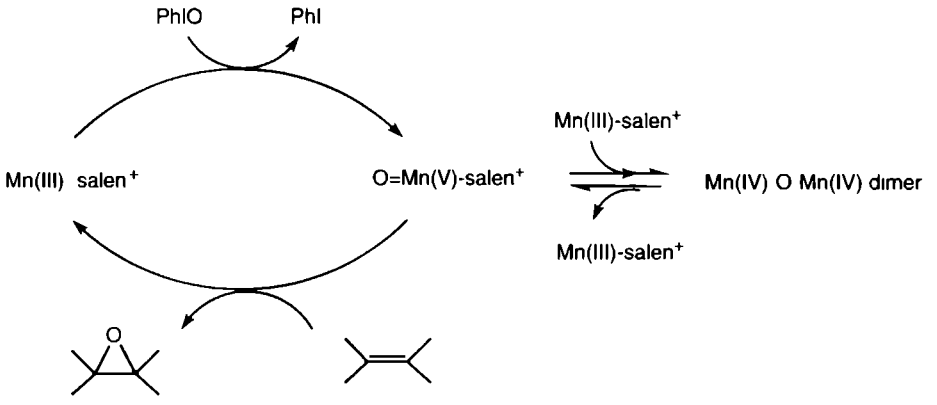
3

Several catalytic studies have been done with salen and salophen (**3**) ligands coordinated to a variety of transition metals including manganese, nickel, chromium, iron, and cobalt [8i,h,l,p,q,s,22] The most successful of these complexes are the Ni(II) (Burrows) and Mn(III) complexes (Kochi, Jacobsen, and Katsuki) in conjunction with NaOCl, or iodosylbenzene as oxidant In 1983, Kochi and co-workers showed that chromium(III) salen complexes were able to epoxidize alkenes with iodosylbenzene as oxidant [8s] This initial work with salen ligands led to investigations with the other metals described above Salen was initially chosen as an appropriate ligand because it has a number of similarities to the porphyrin macrocycle Like the porphyrin ligand, salen is planar and capable of complexing a variety of metals in a rigid square planar geometry Like porphyrin, salen when doubly deprotonated, has a formal charge of -2 An advantage of salen-type ligands is that they are simpler to prepare and to modify than are porphyrin ligands, which is an important consideration in the design of an efficient catalyst They are however, potentially less stable than porphyrins due to oxidative attack on the exposed oxygen atoms on the benzene ring

As an extension of their studies on Cr(III) salens as catalysts, Kochi and co-workers were able to show that Mn(III) salen complexes in conjunction with iodosylbenzene were even better epoxidation catalysts [8q] Mn(III) salen complexes could catalyze the epoxidation of electron-rich and electron-poor alkenes in fairly good yields as opposed to the Cr(III) salen complexes which only epoxidized electron-rich alkenes in poor yields [8s]

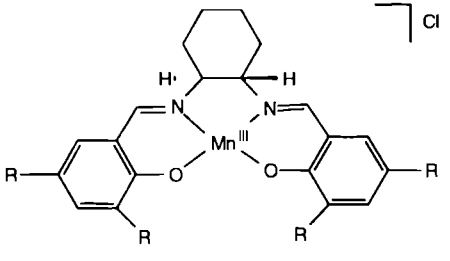
On the basis of kinetic, spectroscopic, and ^{18}O-labeling experiments, it was shown that the active metal-oxygen complex was probably an oxo-complex, described as O=Mn(V)-salen,

which is analogous to the Mn(V)=O species suggested for porphyrins The isomeric structure, O=Mn(IV)-(salen$^{\cdot+}$), however, cannot be ruled out as a possible oxidizing species The oxygen rebound mechanism proposed by Kochi is given in Scheme 2 9

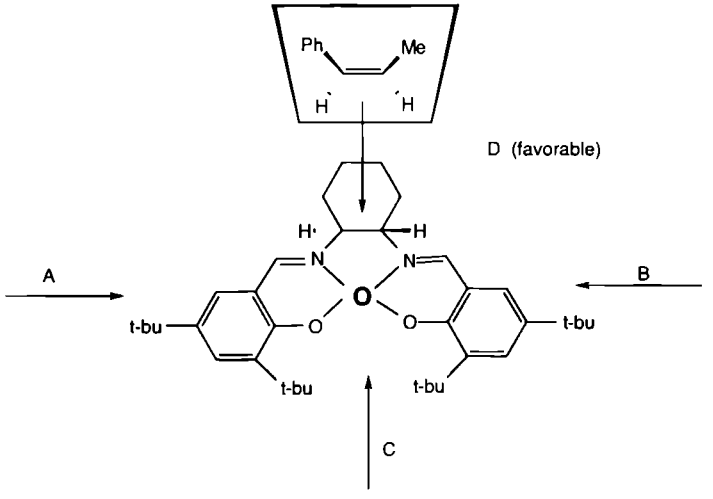


Scheme 2.9 *Oxygen rebound mechanism for the epoxidation of alkenes catalyzed by manganse-salen complexes*

Furthermore, *cis* alkenes are catalyzed by Mn(III) salen complexes to give high yields of *cis*-epoxides with only trace amounts of the *trans* isomer Adding a donor ligand such as pyridine increased the yield of epoxide, especially when electron-poor substrates were used The electronic environment of the Mn(III) ion has an influence on the stereoselectivity of the reaction Electron-withdrawing substituents on the salen ligand, for instance, improved the stereoselectivity, a result which is compatible with a radical intermediate if the rate of ring closure relative to the rate of bond rotation is controlled by the electron deficient manganese center To date, the chiral Mn(III) salen type catalysts (**4**) designed by Jacobsen and co-workers have afforded the highest ee's for epoxides from non-functionalized *cis*-alkenes such as *cis*-β-methylstyrene [6a 8f 8h] Asymmetric epoxidation of alkenes by chiral porphyrins is also possible and has been recently reviewed [6f] The salen ligand system, however, is easier to modify asymmetrically than the porphyrin ligand and chiral modifications on the salen can be made closer to the metal center where oxygen transfer occurs (see e g **4**) than in the case of the porphyrin molecule



With chiral Mn(III) salen catalyst **4,** e e 's of 90% have been achieved with a selective series of non-functionalized alkenes Furthermore, with the addition of the *t* butyl groups on the benzene rings, the catalyst is quite stable even in the presence of sodium hypochlorite which was used by Jacobsen as the oxidant What is remarkable about this catalyst is the fact that it, while chiral, is only slightly asymmetric From the crystal structure of the catalyst it is possible to see that the phenyl groups, which make up the chiral portion of the molecule, lie only slightly above and below the plane of the molecule [6e] Despite this lack of obvious asymmetry, high e e 's are obtained with some *cis*-alkenes The mechanism for this face selection has been explained by steric hindrance of all but one of the interactions of the alkene with the catalyst [6d] This idea is illustrated in Scheme 2 10.



Scheme 2.10 *Favorable (D) and unfavorable (A,B C) approaches of the prochiral cis-alkene to the manganese-oxo (represented by* ***O****) plane of the catalyst*

Nickel(II) salen type complexes have also been intensely studied for their potential as epoxidation catalysts with a variety of oxygen atom donors [8 i k l m,p] Burrows has investigated the efficacy of Ni(II) salen catalysts in combination with iodosylbenzene or sodium hypochlorite Epoxide yields from electron-rich alkenes were fairly good (44% for styrene with a conversion of 98%), but the catalysts were rapidly degraded, especially in the case where NaOCl was used as oxidant The loss of *cis/trans*-stereochemistry in these reactions, and the presence of small amounts of byproducts that were formed as a result of the breaking of the C=C bond, point to a mechanism which involves the attack of a radical species on the alkene Kochi[8p] used Ni(II) cyclam complexes in conjunction with iodosylbenzene to effect the epoxidation of alkenes His studies showed that this catalyst system could epoxidize norbornene with a yield of 47%

2.3 Molecular Oxygen as Terminal Oxidant in the Epoxidation of Alkenes

2.3.1 The nature of molecular oxygen

Until this point, mainly activated, single oxygen atom donors, such as iodosylbenzene, NaOCl, H_2O_2, and alkylhydroperoxides have been mentioned as potential oxidants in epoxidation reactions Molecular oxygen is a separate case and its use as an oxgyen atom donor in epoxidation reactions will be discussed in this section

From an industrial perspective, molecular oxygen is an attractive source of oxgyen atoms because it is readily available, and its use is environmentally-compatible because the byproduct of reactions with molecular oxygen is normally water In addition, molecular oxygen contains, per weight, the largest content of active oxidant compared to other popular oxidants as shown in Table 2 1

Table 2.1 Various oxidants and their active oxygen contents

Oxidant	Active oxidant content/weight %	Waste product
O_2/reductor	50 0	H_2O
H_2O_2	47 0	H_2O
O_3	33 3	O_2
NaOCl	21 6	NaCl
CH_3CO_3H	21 1	CH_3COOH
t BuOOH	17 8	*t*-BuOH
$C_5H_{11}NO_2$[a]	13 6	$C_5H_{11}NO$
NaOBr	13 4	NaBr
$KHSO_5$	10 5	$KHSO_4$
$NaIO_4$	7 5	$NaIO_3$(NaI)
PhIO	7 3	PhI

[a] *N* methylmorpholine *N* oxide

In spite of its attractive qualities as an oxidant, however, molecular oxygen is different from all of the other oxidants listed in Table 2 1 because of the inherent electronic and chemical nature of the O_2 molecule [23a] The terminology used in this thesis to describe the various states of the oxygen molecule is consistent with the standard nomenclature found in the literature The term molecular oxygen is used to refer to the O_2 molecule in its unbound state when the molecule is in the electronic ground state The term dioxygen is used to signify the O_2 moiety in any of several different forms, including those which are unbound or in a combined state No distinction is made between neutral dioxygen and dioxygen in its reduced forms A metal-superoxide or a metal peroxide complex refers to those complexes in which the coordinated dioxygen resembles a superoxide (O_2^-) or a peroxide (O_2^{2-}) anion, respectively

The reason that the use of molecular oxygen in oxidation reactions proves to be so problematic in practice lies in its electronic nature Molecular oxygen is paramagnetic and in the

ground state has a triplet spin ($^3\Sigma_g^-$). The two lowest lying electronic states are the singlet states lying 22.53 and 37.51 kcal/mol above the ground state, respectively. Because organic substrates normally have a closed shell singlet spin state, direct interaction between an organic substrate and molecular oxgyen (in the triplet spin ground state) is spin forbidden. Moreover, O_2 has a bond order of two. If one or two electrons is added to molecular oxygen, superoxide or peroxide is formed, respectively, with superoxide having a bond order of 1.5 and peroxide a bond order of 1.0. In order for molecular oxygen to be able to react with an organic substrate, it must first be reduced to either the superoxide or the peroxide form The overall reduction of O_2 to water is a four electron process that is highly exothermic with ΔG^o = -113.5 kcal/mol which makes molecular oxygen a powerful oxidizing agent. The first reduction of O_2 to HO_2·, however, is an endothermic process, owing mostly to the large reduction in O-O bond strength upon going from O_2 to HO_2·. The other difficulty associated with the use of molecular oxygen in oxidation reactions is the fact that after the first reduction step, the reaction is highly exothermic and often difficult to control, leading to over-oxidation of the substrate and poor selectivity in the oxidation products that are formed.

2.3.2 Catalytic epoxidation of alkenes by molecular oxygen

In spite of these problems, there has been a great deal of interest in developing catalytic systems that can utilize molecular oxygen as the oxidant. These investigations are not only of interest foi industrial processes, but also for the insight they can provide into biological oxidation chemistry, including binding of oxygen to transition metals and oxygen transfer mechanisms Because of their analogous structure to the active sites found in enzymatic systems, porphyrins have been widely investigated for their ability to activate O_2 in the presence of a reductant One of the first attempts to mimic the complete cycle of cytochrome P-450 mediated epoxidation was reported by Tabushi in 1979.[23b] In that system, cyclohexene was oxidized to cyclohexanol and 2-cyclohexen-1-ol (ratio 80/20) in the presence of molecular oxygen, sodium borohydride, and Mn(III)TPP. Cyclohexene oxide was rapidly converted to the alcohol by $NaBH_4$ and was therefore not detected as one of the reaction products. While it was presumed that the reductive activation of dioxygen had occurred, with the subsequent formation of a manganese-oxo species, later work showed that the actual mechanism involved the formation of an alkylmanganese complex arising from the reaction of a manganese (II) complex with the alkene.[24] In the case where cyclohexene was oxidized by sodium borohydride and oxygen in the presence of Rh(III) porphyrin as catalyst, the main product was cyclohexanol.[25] This result suggests that the reaction can be viewed as a catalytic hydration of alkenes rather than the epoxidation of the alkene and subsequent reduction to the alcohol as in the Mn(III) porphyrin case.

When Tabushi replaced $NaBH_4$ by another reducing agent such as H_2/colloidal platinum, epoxides were formed in the presence of Mn(III) porphyrins and O_2.[26] In that system, geraniol acetate was epoxidized at the trisubstituted double bond with total turnovers of 1000-2000 A major drawback was the concurrent production of water on the Pt surface Similar difficulties were experienced with a system developed in our laboratory that utilized H_2/colloidal platinum that was dispersed inside vesicles.[27] The Mn(III) porphyrin molecule was anchored in the bilayer of the vesicle to separate it from the source of electrons Nevertheless, the limiting factor

was again the formation of water on the platinum surface. Tabushi subsequently developed a catalyst system that utilized a NADH analogue to replace the H_2/colloidal platinum as the source of electrons.[28] In this system, the rate of epoxide formation increased 6-fold while the H_2O/epoxide ratio was reduced to 2.

Other reducing agents have been used as electron sources for the reductive activation of oxygen by metallo-porphyrins.[29,30] In a two-phase system containing Mn(III)TPP and ascorbic acid,[29] styrene was converted to styrene epoxide, and *cis*-stilbene afforded a mixture of *cis*- and *trans*-stilbene.

When ascorbic acid was replaced by zinc powder in acetic acid, cyclohexene was oxidized to the corresponding epoxide by Mn(III)TPP which gave 75 turnovers.[30b] *N*-methylimidazole was a required co-factor in that reaction, acting as an axial ligand for the manganese center of the porphyrin.

While metallo-porphyrins have been widely investigated for their ability to carry out the reductive activation of molecular oxygen, only a few studies have been carried out on other transition metal complexes such as metallo-salen complexes and more recently on nickel acetylacetonate derivatives. Using a Mn(III) salen complex, Horwitz and co-workers were able to electrocatalytically epoxidize alkenes by molecular oxygen.[31] The Mn(III) salen was first electrolytically reduced to Mn(II) salen, which subsequently bound molecular oxygen much in the same fashion as proposed for Mn(II) porphyrins. The reported number of turnovers was very low With cyclohexene as substrate, only 4 turnovers of the catalyst were achieved. Elias and co-workers used a Ni(II) tetrahydro-salen complex to achieve the reductive activation of molecular oxygen and the subsequent oxidation of triphenylphosphine.[32]

More recently, Mukaiyama and co-workers have published several reports[33] that describe the epoxidation of alkenes by molecular oxygen in the presence of a primary alcohol or an aldehyde and an appropriate catalyst such as a nickel-, manganese-, iron-, or vanadium acetylacetonate type complex. They were able to obtain high yields of epoxides for a variety of alkenes, with trisubstituted alkenes being the most reactive Furthermore, Mukaiyama's conditions proved to be suitable for carrying out Baeyer-Villager reactions of ketones to give lactones.[34]

While the use of molecular oxygen as the oxidant in epoxidation reactions is a desirable goal in the development of new epoxidation processes, it remains problematic, the most obvious dilemma being the need for sacrificial electrons for the total reductive activation of oxygen There is, however, a vast array of potential electron sources that have not been explored, leaving this area of investigation open for many new chemical insights and discoveries.

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A Manganese(III) Porphyrin/Rhodium(III) Bipyridine/Formate Catalyst System for the Reductive Activation of Molecular Oxygen

3.1 Introduction

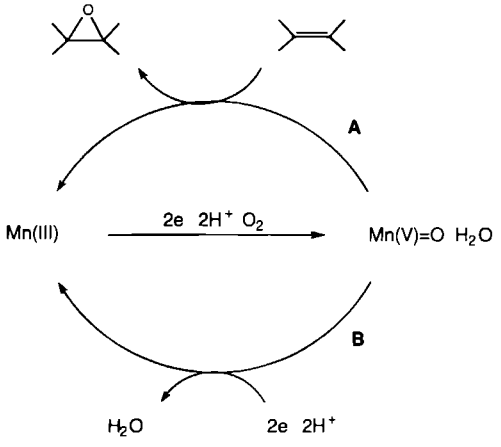
The structure and function of a class of enzymes called monooxygenases have been the inspiration for the design of some synthetic catalytic systems capable of the reductive activation of molecular oxygen.[1-8] Monooxygenases are responsible for the enzymatic transformation of many endogenous substrates as well as xenobiotics. Organic substrates are functionalized by these enzymes to increase their solubility and to facilitate their excretion from the body Cytochrome P-450 is a monooxygenase that, among other reactions, catalyzes the epoxidation of alkenes.[9,10] In general terms this process can be described by equation (1).

$$R + 2H^+ + 2e^- + O_2 \rightarrow RO + H_2O \quad (1)$$

In the case of cytochrome P-450, the two electrons are provided by NAD(P)H which reduces cytochrome P-450 reductase.[10,11] The exquisite control rendered by the enzyme system which delivers precisely two electrons to the Fe(III) center at the right time during the catalytic cycle, is difficult to mimic in the laboratory, but it is this step, *i.e.* the reduction of the Fe(III) or Mn(III) center (in the case of enzyme mimics) to the corresponding Fe(II) or Mn(II) ion that is one of the crucial steps in the catalytic cycle.[1] Attempts described in the literature to utilize molecular oxygen as the oxidant in conjunction with a reductant have only been marginally successful, largely due to the inability to control the number of reducing equivalents.[4,8] Too many reducing equivalents in the vicinity of the Mn(V)=O species will reduce it to Mn(III) and water, with the result that no oxidation products are formed (Scheme 3.1)

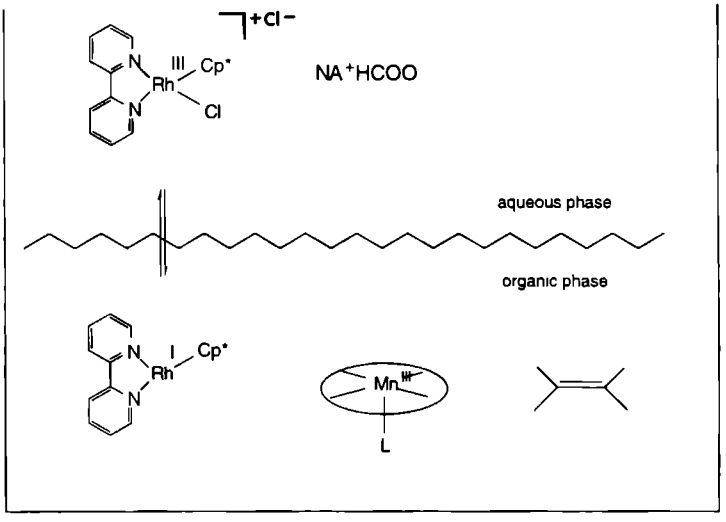
Previous investigations in our laboratory made use of vesicle preparations for modeling the complete catalytic cycle of cytochrome P-450 and for controlling the electron flow to the Mn(III) porphyrin [8] In a vesicle preparation, the reactants are kept separated from one another by the nature of the bilayer structure. In the course of these investigations it was discovered that the rhodium complex [Rh(III)bipyCp*Cl]Cl (bipy = 2,2'-bipyridine, Cp* = η^5-C_5Me_5) was able to efficiently catalyze the reduction of Mn(III) porphyrin to Mn(II) porphyrin by sodium formate [12] Because our goal was to develop a laboratory scale synthetic method for the

epoxidation of alkenes using molecular oxygen as the oxidant it was desirable to simplify the reaction conditions without decreasing the reactivity of the catalyst



Scheme 3.1 *Productive (A) and unproductive (B) pathways in the reaction of the Mn(V)=O species*

We chose a system that imposed some order on the components of the reaction, but did not require the use of vesicles The two-phase reaction system with both hydrophilic and hydrophobic regions separates the catalyst from the electron source The rhodium bipyridyl complex with the rhodium ion in the +3 state is ionic and soluble in the aqueous phase while the alkene substrate and Mn(III)TPP catalyst are soluble in the organic phase The reduced (neutral) rhodium (I) complex migrates into the organic layer where it can subsequently reduce the Mn(III)TPP By exploiting the different solubilities of the oxidized and reduced rhodium species we are able to achieve a degree of separation between the electron source and the manganese porphyrin In the two phase system described here, Mn(III)tetraphenylporphyrin is the catalyst and Rh(III)bipyCp*Cl, in conjunction with sodium formate, is the source of electrons Because of different solubilities in the oxidized and reduced states, the Rh(III)bipyCp*Cl complex acts as a phase-transfer catalyst (Scheme 3 2)



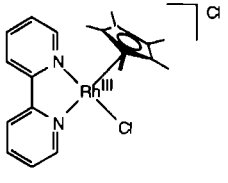
*Scheme 3.2 Representation of the two phase catalytic system with Mn(III)TPP as catalyst and the cationic Rh(III)bipyCp*Cl acting as a co-reductant and as a phase-transfer catalyst*

3.2 Results and discussion

3.2.1 Synthesis

5,10,15,20-Tetraphenylporphyrin (H_2TPP) was prepared by the condensation of benzaldehyde and pyrrole in refluxing propionic acid Metal insertion was carried out in DMF with Mn(II)OAc_2 in the presence of an excess of chloride ion [Mn(III)TPP]Cl was isolated as a dark green crystalline solid

The rhodium dimer precursor $[RhCp^*Cl]_2Cl_2$ was prepared by refluxing hydrated $Rh(III)Cl_3$ in hexamethyl Dewar benzene The product was isolated as a reddish brown powder To this rhodium dimer was added dropwise 0 5 mole equivalents of 2,2 -bipyridine that was dissolved in methanol The resulting pale brown solution turned bright orange and the Rh(III)bipyCp*Cl complex **1** was isolated by precipitation with ether and filtration to give a vivid yellow powder



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3.2.2 Reduction of Mn(III) tetraphenylporphyrin under two-phase conditions

In Chapter 2 the reductive activation of molecular oxygen by cytochrome P-450 and model systems using Mn(III) porphyins was described. A crucial step in this sequence is the reduction of the metal center (usually iron or manganese) from the +3 oxidation state to the +2 state. This step is critical because Mn(III)TPP is not capable of binding molecular oxygen. In the reduced Mn(II) state, molecular oxygen binds to the metal, and the addition of an electron and two protons completes the sequence of reactions to form the active Mn(V)=O species.[1] In order to determine the optimal reaction conditions for epoxidation, we investigated the efficacy of the Rh(III)bipyCp*Cl / formate couple to reduce Mn(III)TPP to Mn(II)TPP under two-phase conditions.

When 2 cm^3 of a 10^{-5} $mol.dm^{-3}$ solution of Mn(III)TPP in dichloromethane was placed in a quartz cuvet and treated with 0.5 cm^3 of an aqueous solution of sodium formate (0.5 $mol.dm^{-3}$) and Rh(III)bipyCp*Cl (5.0 $mmol.dm^{-3}$) (pH 8.0) at 40 °C under an atmosphere of argon, we observed, after several minutes, an intense green coloring in the organic phase. The UV-visible spectrum of this solution showed that the Soret band at 470 nm had disappeared and that a new absorption band at 441 nm had formed (Figure 3.1). This new absorption band is characteristic of a Mn(II)TPP complex In the absence of the rhodium complex or sodium formate, no reduction took place.

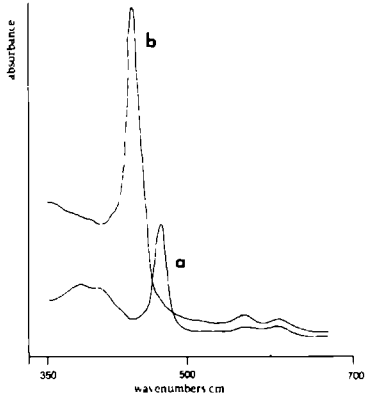
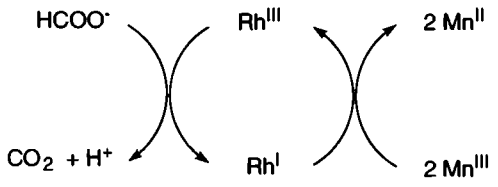


Figure 3.1 *UV-vis absorption spectrum of a solution of Mn(III)TPP (10^{-5} $mol.dm^{-3}$) in dichloromethane after being treated with a sodium formate solution (0.5 $mol.dm^{-3}$), without Rh(III)bipyCp*Cl (a) and with Rh(III)bipyCp*Cl (b) T= 40 °C, pH = 8.0.*

The proposed mechanism for the reduction of Mn(III)TPP by the Rh(III)bipyCp*Cl/formate couple is shown in Scheme 3.3.



Scheme 3.3

Although the reduced Rh(I) species is potentially a two electron reductant, it is capable of reducing Mn(III)TPP, a one-electron substrate The Rh(II) species thus formed is able to reduce another molecule of Mn(III)TPP, or form a dimeric Rh(II) species which would disproportionate into the more stable Rh(I) and Rh(III) forms [13]

The two-phase system precluded carrying out kinetic studies on the reduction of Mn(III)TPP, but the efficacy of the reduction could be measured by determining the percentage of Mn(II)TPP formed after a predetermined period of time The effect of the concentration of Rh(III)bipyCp*Cl on the reduction of Mn(III)TPP to Mn(II)TPP is shown in Figure 3 2

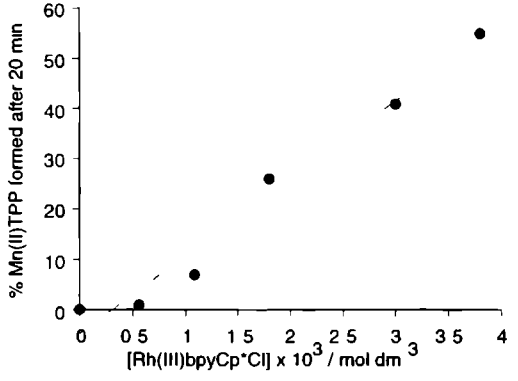


Figure 3.2 *Effect of Rh(III)bipyCp*Cl concentration on the reduction of Mn(III)TPP [Mn(III)TPP] = 1 0 x 10⁻⁵ mol dm⁻³, pH = 7 5, T = 40 °C, 2 0 cm³ trichloroethane, 1 0 cm³ of an aqueous solution (0 5 mol dm⁻³) sodium formate, argon atmosphere*

The reduced rhodium complex must cross the aqueous/organic interface, therefore, a large excess of the rhodium complex is necessary for the reduction of Mn(III)TPP to occur efficiently From Figure 3 2 it can be seen that a linear relationship exists between the concentration of Rh(III)bipyCp*Cl and the rate of formation of Mn(II)TPP from Mn(III)TPP It can also be seen that a minimum amount of rhodium complex (0 5 x 10⁻³ mol dm⁻³) is required for the reaction to occur

Effect of additives on the reduction reaction

A number of components are present during the actual epoxidation reaction, and the effect of each of these additives on the reduction of Mn(III)TPP was investigated The alkene substrates themselves did not affect the reduction reaction, nor did the presence of benzoic acid anhydride, which is used to facilitate the splitting of the oxygen-oxygen bond to form the Mn(V)=O species (see Chapter 2) A marked effect, however, was observed on the reduction reaction when imidazole was present in the solution Imidazole is added to the reaction mixture because it acts as an axial ligand that binds to the manganese center of the tetraphenylporphyrin macrocycle An axial ligand is needed to favor heterolytic cleavage of the oxygen oxygen bond and to stabilize the Mn(V)=O species that is formed as the result of the reductive activation of dioxygen [14,15] As can be seen in Figure 3 3, however, the presence of even a small amount of imidazole in the aqueous phase severely inhibits the reduction of Mn(III)TPP

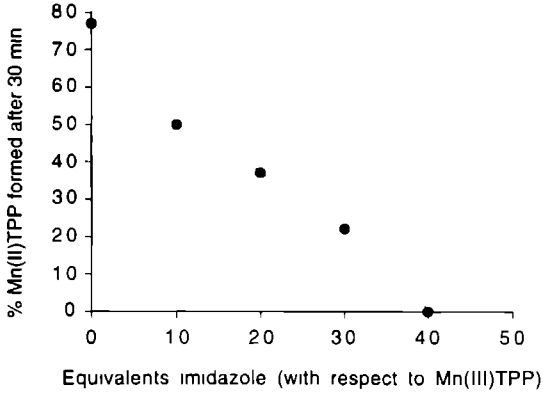
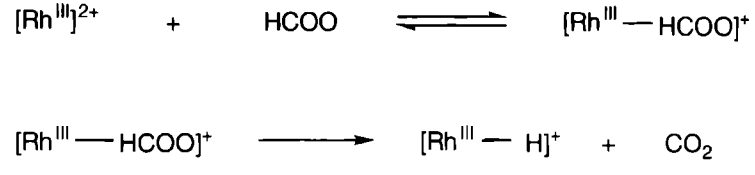


Figure 3.3 *Inhibition of the reduction of Mn(III)TPP to Mn(II)TPP by imidazole under two phase conditions, under an argon atmosphere For reaction conditions see Figure 3 2 [Rh(III)bipyCp*Cl] = 4 0 x 10 ^{3} mol dm ^{3}*

Forty equivalents of imidazole (with respect to the amount of Mn(III)TPP) are sufficient to completely inhibit the reduction of Mn(III)TPP to Mn(II)TPP This inhibition is most likely due to the fact that imidazole competes for the coordination site on the rhodium atom which must be occupied by formate in order for the rhodium species to be reduced The mechanism for the reduction of Rh(III)bipyCp*Cl to the Rh(III)hydride was proposed by Steckhan and co workers [16] and is shown in Scheme 3 4



Scheme 3.4

From Scheme 3.4 it can be concluded that ligands which can successfully compete for a coordination site on the rhodium atom can inhibit or block the formation of the hydride complex. To avoid this complication, other imidazoles, modified with long alkyl chains, were tested for their effect on the reduction reaction. These imidazoles are only soluble in organic media. They are, therefore, not present in the aqueous layer and are unable to inhibit the formation of the Rh(III) hydride. Both *N*-cetylimidazole (C_{16} alkyl chain) and *N*-decyl-imidazole (C_{10}) had no inhibiting effect on the reduction of Mn(III) to Mn(II) not even in amounts as high as 100 equivalents (with respect to Mn(III)TPP) (Figure 3.4).

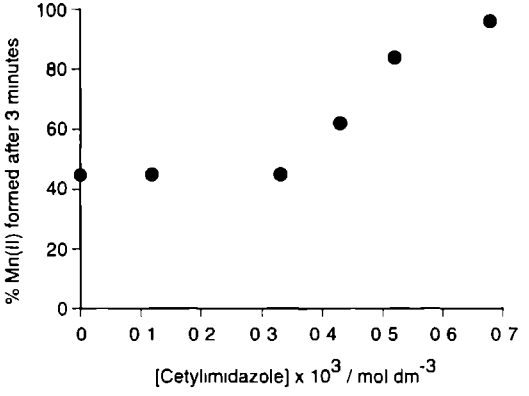


Figure 3.4 *Percent Mn(II)TPP formed after 3 minutes vs. the concentration of N-cetylimidazole For reaction conditions see Figure 3 2 [Rh(III)bipyCp*Cl] = . 4.0 x 10^{-3} mol.dm^{-3}.*

Once the hydride is formed, competing coordinating ligands appear not to inhibit the reduction of Mn(III)TPP. This result is in agreement with the proposed mechanism for the formation of the rhodium-hydride as illustrated in Scheme 3.4. In fact, as can be seen in Figure 3.4, the presence of long-chain imidazoles, increased the rate of the reduction of Mn(III)TPP. At low concentrations, between zero and 0 32 mol.dm^{-3} *N*-cetylimidazole, no enhancement of the reduction of Mn(III)TPP to Mn(II)TPP was observed, but at higher concentrations, there appears to be a linear correlation between the concentration of cetylimidazole and the efficiency at the which the Mn(III) central metal atom was reduced to Mn(II) by the Rh(III)bipyCp*Cl / formate system The unexpected effect of the cetylimidazole on the reduction of Mn(III)TPP can be explained if the orientation of the Mn(III)TPP molecules at the water/dichloromethane interface is assumed to be as is depicted in Figure 3.5

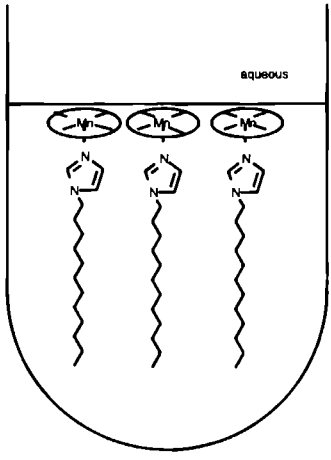


Figure 3.5 *Proposed orientation of the complex between Mn(III)TPP and N-cetylimidazole at the water/dichloromethane interface*

Previous work by Kolle[16] and Steckhan[17 18] has demonstrated that the reduction of rhodium bipyridyl complexes by formate is dependent on the pH of the aqueous solution Kolle found that in acidic pH (< 7 5), the reduction of the Rh(III) complex to Rh(I) was irreversible, presumably because the Rh(I) species is protonated

To study the effect of the pH of the aqueous layer on the reduction of Mn(III)TPP to Mn(II)TPP we looked at the amount of Mn(II)TPP that was formed in the organic layer after 3 minutes at varying pH The results are shown in Figure 3 6

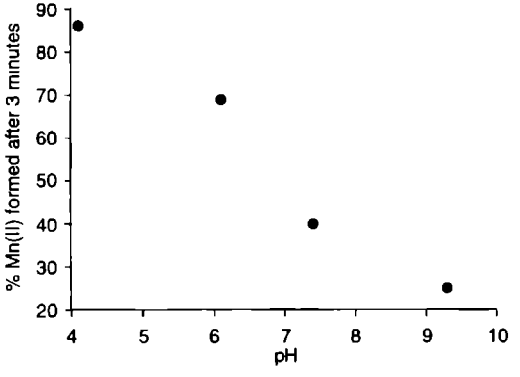


Figure 3.6 *Amount of Mn(II)TPP formed (shown as percentage) after 3 minutes at varying pH values of the aqueous layer For reaction conditions see Figure 3 2 [Rh(III)bipyCp*Cl] = 4 0 x 10 ^{3} mol dm ^{3}*

At pH 4 0, almost 90% of Mn(III)TPP was reduced to Mn(II)TPP after three minutes At pH 9 4 only 22% of Mn(II)TPP was formed after the same period of time Previous work in our laboratory on Rh(III)bipyCp*Cl complexes that were anchored in vesicle systems showed a decrease in activity at lower pH,[12] whereas in the two-phase system described here we found that at low pH the reduction of Mn(III)TPP to Mn(II)TPP was enhanced This result can be explained by the fact that the pH strongly influences the nature of the rhodium species that are formed in aqueous solution

To investigate the rhodium species that are present in solution at varying pH, UV-vis spectra were taken of Rh(III)bipyCp*Cl and formate in water at different pH values At low pH (pH = 4 0), the UV-vis spectrum initially showed a peak at 530 nm which gradually disappeared and was replaced by a peak at 610 nm Due to the acidic conditions, the peak at 610 nm can most probably be ascribed to the protonated Rh(I) complex (which is identical to the Rh(III) hydride) In basic solution, (pH 7 5 9 5) the λ_{max} is at 511 nm which corresponds to the Rh(I) complex that has been reported in the literature[16] (Figure 3 7) The Rh(III)-hydride, which is present in acidic solution appears to be more efficient at reducing Mn(III)TPP to Mn(II)TPP than is the Rh(I) complex which is formed in basic solution Both species, however, are able to reduce the Mn(III) atom, albeit at varying degrees of efficiency as illustrated in Figure 3 6

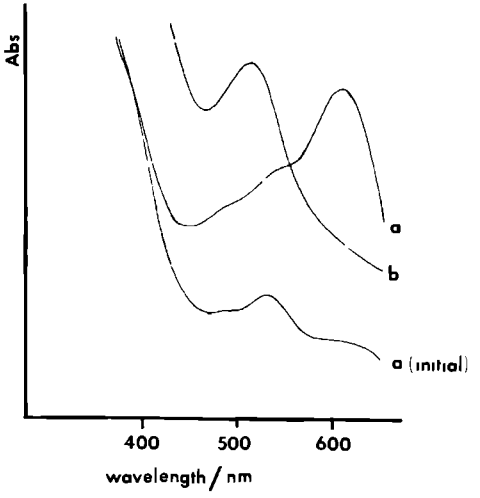


Figure 3.7 *UV-vis spectra of Rh(III)bipyCp*Cl with Na^+HCOO^- in acidic solution (pH = 4) (a), and basic solution (pH = 9) (b)*

Using UV-vis spectroscopy, we attempted to observe the presence of the Rh(I) species in the organic layer under two-phase conditions Only after all of the Mn(III)TPP had been reduced to Mn(II)TPP did a band at 520 nm appear, which is characteristic of the Rh(I) complex, taking in account the differences in solvent

Although the rhodium bipyridyl complex itself acts as a phase transfer catalyst under the two-phase system described here, we were interested in determining the influence that a standard phase transfer-catalyst such as a quaternary ammonium salt would have on the

reduction of Mn(III)TPP. The effect of adding a catalytic amount of benzyltributylammonium chloride to the two-phase solution are shown in Figure 3.8.

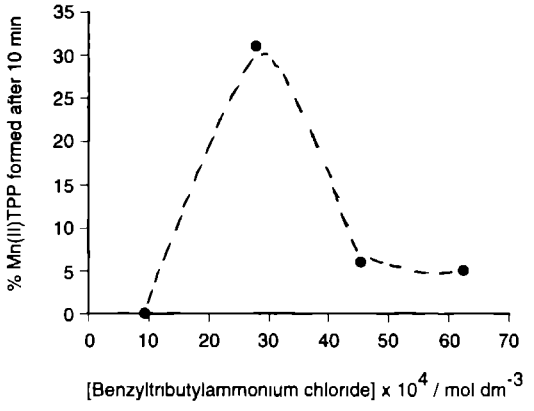


Figure 3.8 *Effect of a phase transfer catalyst (benzyltributylammonium chloride) on the reduction of Mn(III)TPP to Mn(II)TPP. For reaction conditions see Figure 3.2. [Rh(III)bipyCp*Cl] = 4.0 x 10^{-3} mol.dm^{-3}.*

A small amount of phase transfer catalyst had no effect on the rate of reduction Mn(III)TPP to Mn(II)TPP. In a 3.0 mmol.dm^{-3} solution of phase transfer catalyst, however, the amount of Mn(II)TPP formed after ten minutes was markedly enhanced. More concentrated solutions of benzyltributylammonium chloride inhibited the reduction of Mn(III)TPP to Mn(II)TPP, probably due to the increased concentration of chloride ion in solution which will shift the equilibrium of the formation of the Rh(III)-HCOO species to the left (see Scheme 3.4).

3.2.3 Epoxidation

Once the appropriate reaction conditions for the efficient reduction of Mn(III)TPP had been determined it was possible to carry out epoxidation reactions under two-phase conditions. Epoxidation reactions were carried out with several alkene substrates under different oxygen pressures and in the presence or absence of benzoic anhydride. The results are summarized in Table 3.1.

Table 3.1 Epoxidation results with Mn(III)TPP/Rh(III)bipyCp*Cl/formate in a two-phase system[a]

Substrate	$[(PhCO)_2]/M^{-1}$	$p(O_2)$ / mmHg	Turnover number[b]
α-Pinene	0 05	160	30
Nerol	0 05	0	<1
Nerol	0.05	160	18
Nerol	0 05	760	17
Nerol	0	160	8
cis-Stilbene	0 05	160	42

[a]Reaction conditions 0 285 mol dm^{-3} alkene, 0 1 mmol dm^{-3} MnTPP, 5 0 mmol dm^{-3} Rh(III)bipyCp*Cl, 10 0 mmol dm^{-3} *N*-decylimidazole, 0 5 mol.dm^{-3} sodium formate, 2 0 cm^3 trichloroethane/H_2O, 1 1,v/v, 40 °C, pH = 8 0

[b]Total turnovers during the course of the reaction

The highest turnover numbers were obtained in the presence of benzoic anhydride Benzoic anhydride has been shown previously in investigations reported in the literature[1,14] to assist in the splitting of the oxygen-oxygen bond. This mechanism is illustrated in Chapter 2, Scheme 2.6 The oxygen pressure did not appear to have a large influence on the reaction, with approximately equal amounts of nerol epoxide being formed under 1.0 atmosphere of oxygen and under air. In all cases, the formation of epoxide stopped after 30-60 minutes. Even running the reaction for several hours to overnight did not result in an increase in epoxide yield. We presumed that the Mn(III)TPP was still viable due to the characteristic dark green/brown color of the reaction mixture indicative of Mn(III)TPP. Spectral evidence, however, showed that the Mn(III)TPP catalyst was completely degraded after one hour of reaction time. The characteristic Soret band at 470 nm in the UV-vis spectrum was gone, indicating complete decay of the complex. The degradation of the Mn(III)TPP catalyst was followed over time and the results are shown in Figure 3.9.

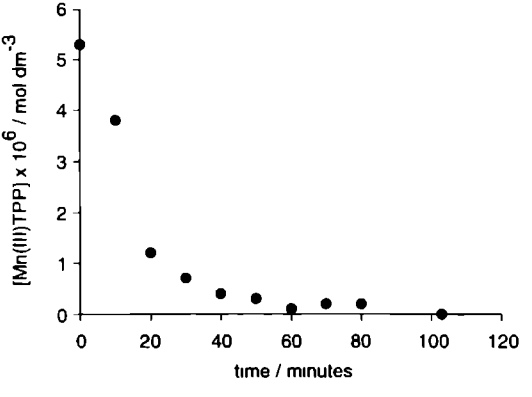


***Figure 3.9** Decay of Mn(III)TPP under the reaction conditions used for epoxidation. (See Table 3 1).*

This rapid degradation of the Mn(III) porphyrin catalyst is quite remarkable in light of the fact that Mn(III)TPP has been shown to be stable under a variety of oxidizing conditions.[19,20] We hoped to improve the number of turnovers and increase the yield of epoxide formed by replacing the Mn(III)TPP with a more robust catalyst. We chose Mn(III)TPP complexes that are modified with electron-withdrawing substituents at the ortho positions in the phenyl rings as well as porphryins with completely substituted phenyl rings as shown in Figure 3.10.

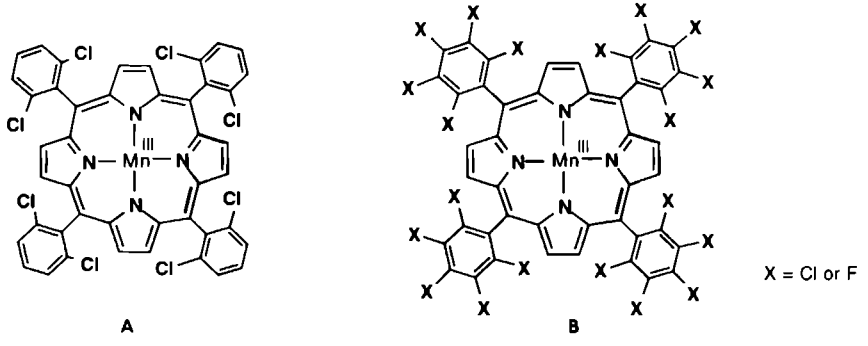


Figure 3.10 *Mn(III)T_2ClPP (A), and MnT_{penta}ClPP, MnT_{penta}FPP (B).*

These so-called "second generation" porphyrins[21-25] are less susceptible to attack at the meso-positions due to both steric effects from the substituents as well as the electron-withdrawing effect which makes the meso-position less favorable to electrophilic degradation. The results of epoxidation reactions carried out with these catalysts are shown in Table 3.2

Table 3.2 Epoxidation results using substituted mangenese porphyrins as catalysts[a]

Porphyrin catalyst	Substrate	Total turnover #
MnT_2ClPP	α-Pinene	3
MnT_2ClPP	Styrene	4
MnT_{penta}ClPP	α-Pinene	0
MnT_{penta}FPP	α-Pinene	8

[a]Reaction conditions 0 285 mol dm^{-3} alkene, 0 1 mmol dm^{-3} Mn(III) porphyrin, 5 0 mmol dm^{3} Rh(III)bipyCp*Cl, 10 0 mmol dm^{-3} *N*-decylimidazole, 0 2 mol dm^{-3} benzoic anhydride, 1 0 cm^3 0 5 mol dm^{3} sodium formate, pH = 8 0, 2 0 cm^3 trichloroethane/$H_2$0, 1 1, v/v, pO_2 = 160 mmHg, 40 °C

Turnovers numbers were not improved for two reasons. All of the catalysts shown in Table 3.2 except for MnT_{penta}FPP decayed within a short period of time (approx 1 hr) in a similar manner to that of Mn(III)TPP. Mn(III)T$_{penta}$FPP appeared to be stable under the reaction

Clearly a strongly oxidizing species is formed during the course of the reaction which is responsible for the degradation of the porphyrin catalysts It is known that rhodium bipyridyl complexes are capable of forming peroxo or superoxo rhodium species in the presence of a reducing agent under basic conditions [27 30] Furthermore, these rhodium-superoxo complexes are able to oxidize Fe(II) to Fe(III) Because our epoxidation system includes a rhodium(III) bipyridyl complex in the presence of a reducing agent we attempted to establish a relationship between the concentration of rhodium complex present in solution and the rate of degradation of the Mn(III)TPP The results are shown in Figure 3 11

It is clear from Figure 3 11 that increasing the amount of rhodium in the reaction mixture increases the degree to which the Mn(III)TPP catalyst is broken down Control reactions determined that the Rh(III)bipyCp*Cl complex in its unreduced state is not responsible for the decay of the porphyrin

There is also some spectral evidence for the presence of a rhodium-superoxo species that forms from the interaction of the reduced rhodium species in the presence of oxygen Two different spectral traces were observed when samples of water (pH = 8 0) containing Rh(III)bipyCp*Cl and formate ion were measured using UV-vis spectroscopy either under argon or in the presence of oxygen The spectrum of the solution containing oxygen also showed after several minutes the appearance of a peak at 600 nm which is indicative of a rhodium superoxo species according to results reported by Addison [27]

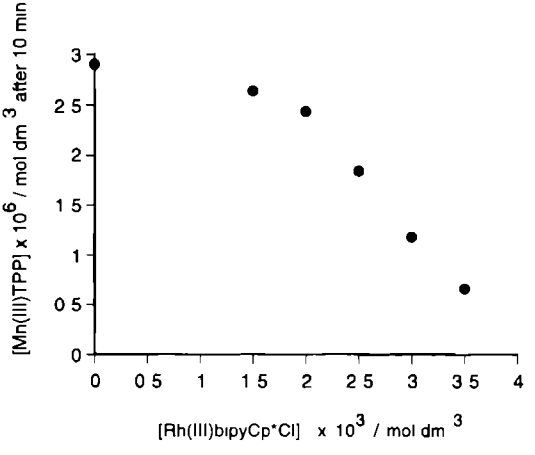


Figure 3.11 *Decay of Mn(III)TPP vs Rh(III)bipyCp*Cl concentration For reaction conditions see Figure 3 2*

If we assume that a rhodium-superoxo species is responsible for the fairly rapid degradation of the Mn(III)TPP catalyst we can try to alter the reaction conditions to prevent the formation of this highly oxidizing species Control experiments showed that in the absence of Mn(III)TPP, no epoxides were formed Therefore, the oxidizing rhodium species that is presumably generated is not capable of epoxidizing the substrate

Because evidence described in the literature[27] states that rhodium bipyridyl superoxo species form under basic conditions, we investigated the epoxidation of α-pinene under conditions of varying pH. The results are shown in Table 3.3.

Table 3.3 Epoxidation results with α-pinene at varying pH[a]

pH of aqueous phase	Total turnover #
4.0	0
5.0	0
6.0	6
7.0	10
8.0	30
9.0	3

[a]Reaction conditions 0.285 mol dm^{-3} alkene, 0.1 mmol dm^{-3} MnTPP, 5.0 mmol dm^{-3} Rh(III)bipyCp*Cl, 10.0 mmol dm^{-3} *N*-decylimidazole, 0.2 mol dm^{-3} benzoic anhydride, 1.0 cm^3 0.5 mol dm^{-3} sodium formate, pH = 8.0, 2.0 cm^3 trichloroethane/H_2O, 1:1, v/v pO_2 = 160 mmHg, 40 °C

These results suggest that the ideal conditions for the reduction of Mn(III) may not translate into ideal conditions for the epoxidation of alkenes. While Mn(III) is more easily reduced to Mn(II) at pH 4 as shown in Figure 3.6, no epoxide was formed at this pH. At higher pH, epoxide is formed, but with concurrently faster degradation of the catalyst. At pH 4.0, the Mn(III)TPP is not degraded, while at pH 9.0, the Mn(III)TPP is degraded after approximately 30 minutes of reaction time.

3.3 Concluding remarks

We have shown that it is possible to carry out the reductive activation of molecular oxygen (and subsequent epoxidation of alkenes) using Rh(III)bipyCp*Cl and formate ion as the source of electrons for the reduction of Mn(III) porphyrin to Mn(II) prophyrin. The epoxidation reactions were run in a two-phase system which was chosen to provide some separation of the Mn(III)TPP catalyst from the reductant. Separation of the electron source from the porphyrin catalyst is necessary to avoid the unproductive pathway, that of the reduction of the active Mn(V)=O species to water, as illustrated in Scheme 3.1. We were able to exploit the different solubilities of the oxidized and reduced forms of the rhodium bypyridyl complex so that it could behave as a phase-transfer catalyst. The rhodium species in the $^{+}3$ state is ionic and soluble in the aqueous phase. As the neutral Rh(I) species the complex migrates into the organic layer where it reduces the Mn(III)TPP to Mn(II)TPP. This slow diffusion of the reduced rhodium complex limits the amount of reducing equivalents in the immediate environment of the Mn(III) porphyrin. Which reduced rhodium species--either the Rh(I) or the Rh(III)-hydride--is present in solution is dependent upon the pH of the aqueous layer. At high pH (= 9), the Rh(I) species is predominant, and reduction of Mn(III)TPP to Mn(II)TPP is slower. At low pH (= 4), the Rh(III)-hydride species is predominant, and the reduction of Mn(III) to Mn(II) of the porphyrin molecule is faster. Because the reduced rhodium complex must cross the organic solvent/water

interface, a 20-fold excess of Rh(III)bipyCp*Cl respective to the amount of Mn(III)TPP is necessary for efficient reduction of Mn(III)TPP to occur

We were also able to show that coordinating ligands such as imidazoles, which are used as axial ligands for Mn(III)TPP, could compete for the site on the rhodium atom that must be occupied by formate ion for the formation of the rhodium hydride to occur This competition by imidazole inhibits the reduction of Mn(III)TPP to Mn(II)TPP Long chain imidazoles, such as *N*-cetylimidazole, that are only soluble in the organic phase, enhanced the rate of reduction, probably by positioning the Mn(III) porphyrin molecules closer to the dichloromethane/water interface (Figure 3 5)

Although we were able to show that Mn(III)TPP can be efficiently reduced to Mn(II)TPP under the two-phase conditions in the presence of Rh(III)bipyCp*Cl and sodium formate, the subsequent epoxidation of alkene substrates proceeded less smoothly Turnover numbers of 30 were achieved for α-pinene and 42 for *cis*-stilbene at pH 8 0 Despite their low values, these turnover numbers are in fact some of the highest reported in the literature for Mn(III) porphyrin catalysts that use molecular oxygen as the terminal oxidant [2-8] For an epoxidation system, however, these numbers are quite low and attempts to improve them were not successful for a number of reasons The Mn(III)TPP catalyst itself was not stable under the reaction conditions Within one hour of reaction time, the Mn(III)TPP molecule was completely degraded Even more robust porphyrins[21-25] such as the "second-generation" ortho-substituted chloro-porphyrins, and the penta-substituted chloro- and fluoro-porphyrins were either completely degraded during the course of the reaction or, in the case of Mn(III)T_{penta}FPP, were unreactive The reason for this fast oxidative degradation of the Mn(III) porphyrin catalysts is most likely due to a rhodium-superoxo species that forms as a result of the interaction between the reduced rhodium bipyridyl complex and molecular oxygen These complexes have been reported in the literature as occurring when Rh(III) complexes are in the presence of a reducing agent and a base [27] The structure of these rhodium-superoxo complexes have been shown to be trans-dimers [27 33 34]

Varying the pH of the aqueous layer did not improve catalyst turnovers Mn(III)TPP was rapidly reduced to Mn(II)TPP at pH 4 0, but no epoxide was formed at this pH At higher pH, in contrast, such as pH 9 0, epoxide was formed, but the Mn(III)TPP catalyst was rapidly broken down In fact, the more basic the aqueous layer was, the faster the porphyrin molecule was degraded The optimum pH for the epoxidation reactions, or that which gave the highest turnover numbers was a pH between 7 and 8

In order to improve the turnover numbers and thus the yield of epoxide produced in the two phase system, it is necessary to inhibit the interaction between the reduced rhodium complex and molecular oxygen The rhodium complex in the $^{+3}$ state appears to be inert to oxygen, so that increasing the rate of electron transfer from the reduced rhodium species to the manganese(III) porphyrin may be a way of increasing catalyst turnover and the overall efficiency of the reaction The work on improving epoxide yields with this system is described in Chapter 4

3.4 Experimental

Materials. Unless otherwise indicated, all reagents were purchased from Aldrich and used as received, except for pyrrole which was distilled before use Trichloroethane and dichloromethane were distilled from $CaCl_2$ and stored over 4Å molecular sieves The water used in the two-phase epoxidation reactions was doubly distilled Alkenes were purified by column chromatography over basic alumina gel (eluent = CH_2Cl_2)

Instrumentation. IR spectra were taken on a Perkin Elmer 1720-X Infra-red Fourier Transform spectrometer GC-analyses were carried out on a Varian 3700 gas chromatograph equipped with a flame ionization detector, (column CP-sil fused silica, 25 m, 25µm diameter) coupled to a Hewlett Packard 3395 integrator UV-visible spectra were taken on a Perkin Elmer Lambda 5 spectrometer Elemental analyses were determined with a Carlo Erba Ea 1108 Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected

Syntheses.

5,10,15,20-tetraphenylporphyrin, H_2TPP. Distilled pyrrole (2 15 g, 0 032 mol) and 0 032 mol of benzaldehyde were added to 120 cm^3 of refluxing propionic acid The mixture was refluxed for 30 min under air and subsequently placed in a refrigerator (4 °C) for several hrs to overnight After filtration, the residue was washed with hot water (50 cm^3) and then with methanol until the washings were colorless The H_2TPP, isolated as a glistening purple powder, was dried under vacuum The porphyrin normally contains between 0-5% 2,3-dihydroporphyrin To remove this impurity, the procedure developed by Barnett *et al* [31] and improved by van der Made[32] was used H_2TPP (1 0 g) was dissolved in refluxing dichloromethane (250 cm^3) and treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (250 mg, 1 1 mmol) in 15 cm^3 of toluene After refluxing for 30 min , the solvent was removed and the remaining purple powder was chromatographed on neutral alumina (200 g) in chloroform The porphyrin fraction was concentrated to 200 cm^3 and 200 cm^3 of methanol was added Further evaporation resulted in precipitation of the desired porphyrin, which was collected by filtration Yield 21% ^{1}H-NMR ($CDCl_3$) δ 8 85 (s, 8H, β-pyrrole), 8 21 (m, 8H, 2,6-phenyl), 7 73 (m, 8H, 3,5-phenyl), 7 69 (m, 4H, 4-phenyl) UV-vis CH_2Cl_2, λ / nm, log (ε / dm^3 mol^{-1} cm^{-1})) 417 (5 65), 482 (3 47), 5 13 (4 60), 549 (3 90), 591 (3 70), 650 (3 70)

Mn(III)TPP·Cl. Mn(III)TPP Cl was prepared from the free ligand, H_2TPP, by adding 0 5 g (2 0 mmol) manganese acetate tetrahydrate to a heated solution of 15 cm^3 *N,N*-dimethylformamide and 1 0 mmol of H_2TPP The solution was allowed to reflux for 30 min or until all the H_2TPP had disappeared The solvent was removed under reduced pressure The residue was dissolved in chloroform (60 cm^3) and stirred for 2 hrs with 60 cm^3 of aqueous sodium chloride (30 g/100cm^3) The chloroform fraction was separated from the water layer, dried and concentrated The residue was redissolved in a minimum amount of methanol and filtered Evaporation of the filtrate yielded pure Mn(III)TPP Cl as a green powder in greater than 90% yield UV-vis (CH_2Cl_2, λ / nm, log (ε / dm^3 mol^{-1} cm^{-1})) 369 (4 73), 398 (4 62), 443 (4 00), 470 (5 02), 575 (3 93), 615 (4 03)

$MnT_{penta}FPP·Cl$, $MnT_{penta}ClPP·Cl$, and $MnT_{2,6}diClPP·Cl$. These compounds were the gift of Dr Jan van Esch, currently of the University of Groningen

[RhCp*Cl]$_2$Cl$_2$. This complex was synthesized according to a literature procedure by Kang, et al [35] Rhodium(III) chloride (1 0 g) was added to 10 0 cm^3 of refluxing hexamethyl Dewar benzene The resulting red/brown solution was allowed to reflux in air for 1 h The reaction mixture was allowed to cool and 30 cm^3 of diethylether was added to precipitate the rhodium dimer product The red/brown product was filtered and washed several time with water, then ether and allowed to dry in air Yield = 88% Physical properties were similar to literature values

[Rh(III)bipyCp*Cl]Cl. A solution of 200 mg [RhCp*Cl]$_2$Cl$_2$ (0 32 mmol) was added to 5 0 cm^3 of methanol and stirred under air at room temperature To this mixture was added dropwise a solution of 2,2 -bipyridine, 107 mg (56 mmol) in 1 0 cm^3 of methanol The resulting mixture turned a bright orange and was stirred for 30 min The solvent was removed under reduced pressure and the residue was redissolved in a minimum of methanol The bright yellow product was precipitated by the addition of cold diethyl ether Yield 99% ^{1}H-NMR ($CDCl_3$) δ 8 93 (d, 2H, H^6,H$^{6'}$), 8 85 (d, 2H H^{3}H$^{3'}$), 8 18 (dd, 2H H^4, H$^{4'}$), 7 81 (dd, 2H H^5, H$^{5'}$), 1 68 (s, 15 H Cp*) UV vis λ_{max} (nm) in H_2O 303, 321 Anal calcd for $C_{20}H_{23}N_2RhCl_2$ H2O C 49 71 H 5 21 N 5 80, found C 49 08 H 5 18 N 5 81

Epoxidation reactions. A Schlenck tube (2 0 cm x 10 0 cm) was charged with 2 0 cm^3 of trichloroethane To the solvent was added in this order, 78 mm^3 (0 60 mmol) alkene, and benzoic anyhydride (0 60 mmol) *N*-cetylimidazole and Mn(III) porphyrin were added to give a solution of 10 0 mmol dm ^{3} and 0 1 mmol dm ^{3}, respectively Sodium formate (1 0 cm^3, pH 8 0) and Rh(III)bipyCp*Cl_2 were added to the reaction mixture to give a final concentration of 0 5 mol dm ^{3} and 5 0 mmol dm ^{3}, respectively The resulting two-phase solution was placed in a 40 °C waterbath and vigorously stirred in air At appropriate intervals the stirring was stopped and an aliquot of the organic layer was taken and analyzed by gas chromatography

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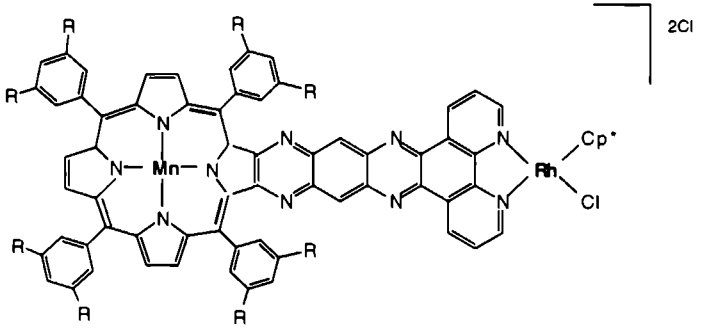
Coupled Manganese(III) Porphyrin/Rhodium(III) Bipyridine Complexes as Catalysts for the Epoxidation of Alkenes by Molecular Oxygen

4.1 Introduction

In Chapter 3 a system that was capable of the reductive activation of molecular oxygen and the subsequent epoxidation of unfunctionalized alkenes was described That system made use of a Mn(III) porphyrin and a Rh(III) bipyridine complex as a redox couple in conjunction with formate ion, applied under two-phase (organic/aqueous) conditions The two-phase system was designed to minimize the number of reducing equivalents (electrons from the reduced Rh(III) complex) that are in the vicinity of the Mn(III) porphyrin at any given time As already discussed in Chapter 3, Section 3 2, the major drawback of this system was the rapid decay of the Mn(III) porphyrin catalyst that occurred under the conditions of the epoxidation reaction

We proposed that a rhodium-superoxo species, formed during the reaction, was the probable agent for the rapid degradation of the manganese porphyrin catalyst To avoid this problem we designed a system in which electron transfer from the reduced rhodium species Rh(I) to the Mn(III) porphyrin would be faster than the formation of the rhodium-superoxo species In the two-phase system, electron transfer was diffusion controlled and thus relatively slow Because the Rh(I) species is reactive toward oxygen (and the Rh(III) species is not), fast transfer of electrons from the reduced rhodium to the manganese is essential to avoid the formation of the superoxo species

In this chapter we describe a catalyst system that utilizes two different complexes (**1** and **2**) in which the Mn(III) porphyrin moiety and the Rh(III) bipyridine moiety are connected by a π-conjugated bridge These complexes were designed to enhance electron transfer between the two metal centers by bringing the two moieties closer together and attaching them *via* a rigid π-conjugated spacer Recent developments in the synthetic chemistry of modified porphyrins by Crossley and co-workers[1] have made it possible to modify the porphyrin molecule into large and sometimes serially connected π-conjugated systems, leading to extensive aromatic ligands



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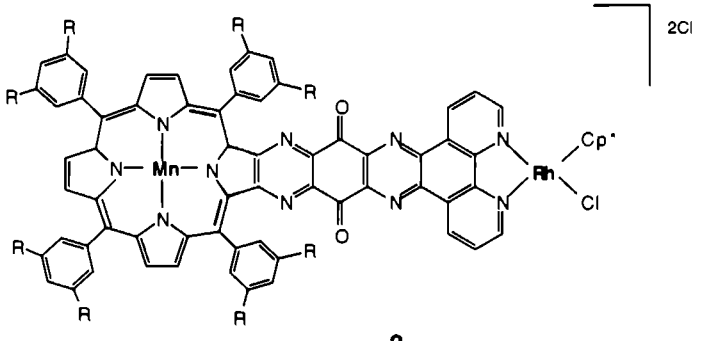


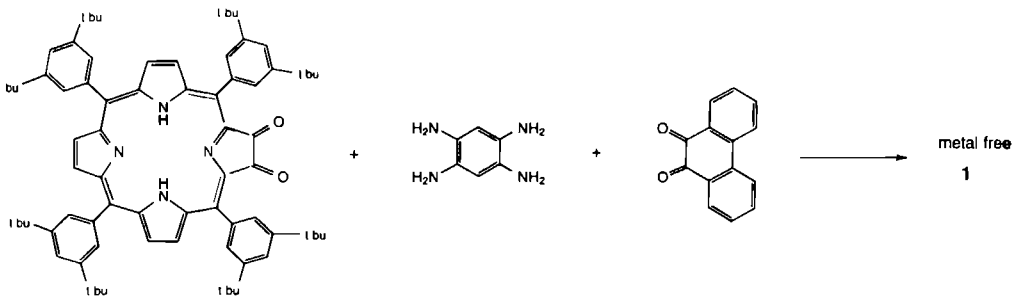
2

R = *t*-butyl

4.2 Results and discussion

4.2.1 Synthesis

The metal-free ligand of complex **1** was prepared as shown in Scheme 4.1.[2]



Scheme 4.1

The condensation reaction of 2,3,5,6-tetraaminobenzene with the diketone derivatives of the porphyrin molecule and phenanthroline afforded the metal-free ligand of **1** [1 3] The Mn(III) ion was subsequently inserted into the porphyrin portion of the molecule by refluxing the ligand with an excess of Mn(II) acetate tetrahydrate in DMF The rhodium portion of the complex was prepared by reacting the manganese(III)-containing ligand of complex **1** with 0 5 mol equivalents of $[RhCp^*Cl]_2Cl_2$ in methanol The metal-containing complex **2** was prepared by refluxing the ligand in DMF with an excess of Mn(II) acetate tetrahydrate After the isolation of the manganese(III)-containing ligand, the rhodium(III) containing part of the complex was prepared by reacting 0 5 mol equivalents of the complex with $[RhCp^*Cl]_2Cl_2$ in methanol

4.2.2 Reduction of the bridged manganese(III) porphyrin/ rhodium(III) bipyridine complexes 1 and 2

Reduction of the Mn(III) ion to Mn(II) in the porphyrin part of complexes **1** and **2** was followed by UV-vis absorption spectroscopy When a $2\,0 \times 10^{-5}$ mol dm^{-3} solution of **1** in methanol (2 0 cm^3) was placed in a quartz cuvet and treated with 30 mm^3 of an aqueous solution of sodium formate (2 5 mol dm^{-3}) at 40 °C under an atmosphere of argon, the peaks at 486 nm (Mn(III) porphyrin) and 430 nm disappeared, and a new band appeared at 440 nm (Figure 4 1) This new band is indicative of the Mn(II) porphyrin [4] In the absence of sodium formate, no reduction took place

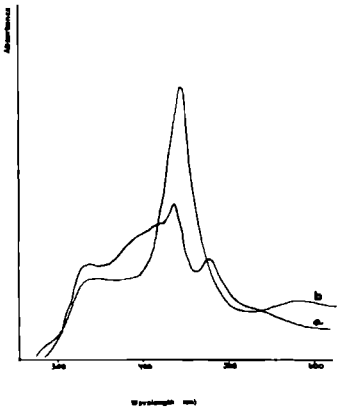


Figure 4.1 UV-vis spectra of 1 in aqueous methanol in the absence (a) and presence (b) of sodium formate [Complex 1] = 2 0 x 10^{-5} mol dm ^{3}, [sodium formate] = 0 035 mol dm ^{3}, T = 40 ^{o}C

As discussed in Chapter 2, a crucial step in the reductive activation of molecular oxygen,and the formation of the Mn(V)=O species for the subsequent epoxidation of alkenes,is the reduction of the Mn(III) metal center to Mn(II) [5] We therefore investigated the conditions under which the Mn(III) porphyrin part of the bridged system in complex **1** could be most efficiently reduced by the rhodium bipyridyl group

The reduction experiments were carried out at several different temperatures in methanol and as can be seen in Figure 4 2 the reduction of Mn(III) to Mn(II) follows zero order kinetics

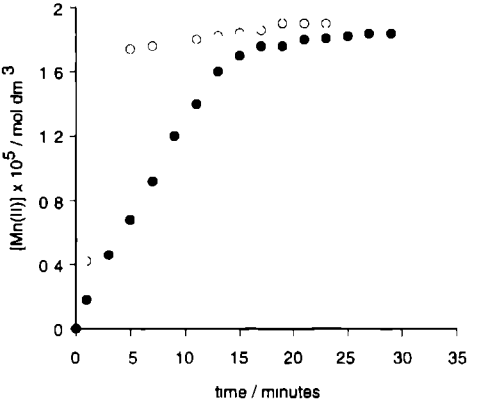


Figure 4 2 The reduction of Mn(III) to Mn(II) in complex 1 by sodium formate in methanolic solution at 26 0 ^{o}C (•) and 40 9 ^{o}C (o) [Complex 1] = 2 0 x 10 ^{5} mol dm ^{3}, [sodium formate] = 0 035 mol dm ^{3} The zero order rate constants for the reactions at 26 0 ^{o}C and 40 9 ^{o}C are (1 05 ± 06) x 10 ^{7} mol dm ^{3} s ^{1} and (4 88 ± 20) 10 ^{7} mol dm ^{3} s ^{1} respectively

The zero order dependence of the reduction of Mn(III) to Mn(II) can be explained from the fact that the rate determining step in the reaction sequence is the reduction of Rh(III) to Rh(I) by sodium formate (as proposed by Steckhan, et al [6]) leading to zero order kinetics in the subsequent step, i e the reduction of Mn(III) to Mn(II)

For purposes of comparison, the reduction of Mn(III) to Mn(II) was followed in a reaction involving the *decoupled* components of the system, i e Mn(III)TPP and Rh(III)bipyCp*Cl in methanolic solution containing sodium formate The result is shown in Figure 4 3

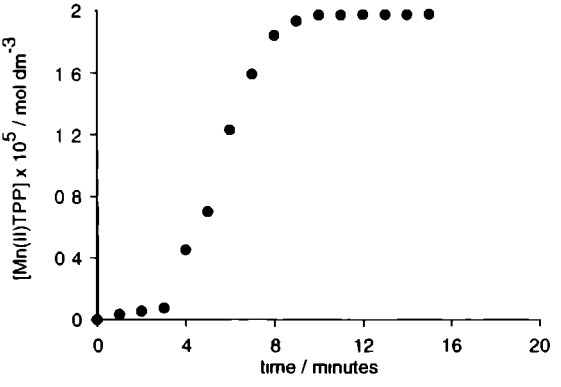


Figure 4.3 *Reduction of Mn(III)TPP by Rh(III)bipyCp*Cl and formate ion in methanolic solution [Mn(III)TPP] = 2 0 x 10^{-5} mol dm^{-3}, [Rh(III)bipyCp*Cl] = 2 0 x 10^{-5} mol dm^{-3}, [sodium formate] = 0 035 mol dm^{-3}, T = 40 6 °C Zero order rate constant = (3 16 ± 15) x 10^{-7} mol dm^{-3} s^{-1}*

Under identical reaction conditions the π-bridged Mn(III)porphyrin / Rh(III)bipyCp*Cl complex **1** was reduced faster than was Mn(III)TPP by the free Rh(III)bipyCp*Cl (compare Figures 4 2 and 4 3) There was also a relatively long induction period (approximately 4 minutes) in the reduction of Mn(III)TPP by Rh(III)bipyCp*Cl / formate that is not present in the reduction of the π-bridged complex **1** The induction period is most likely a result of the need for a sufficient concentration of the Rh(III)-hydride to form before reduction of Mn(III) to Mn(II) can occur (see Chapter 3) This build up of the Rh(III)-hydride species is unnecessary in the reaction mixture with complex **1** because the subsequent reduction of Mn(III) to Mn(II) occurs in the same molecule as the reduction of the rhodium species It appears from these results that the electron transfer from the reduced rhodium complex to the Mn(III) center of the porphyrin moiety is facilitated by coupling the two metal centers together as in complex **1** [7]

When a 2 0 x 10^{-5} mol dm^{-3} solution of complex **2** was placed in a quartz cuvet, and treated with an aqueous solution (30 mm^3) of sodium formate (0 035 mol dm^{-3}) at 28 6 °C under an atmosphere of argon, two changes in the spectrum occurred The absorption at 488 nm increased in intensity and the peak at 400 nm decreased and shifted to the right We interpreted these spectral changes to be indicative of the reduction of the quinone part of the molecule to

either the hydroquinone or the the semiquinone A reduction to the semiquinone is a one electron process that requires no additional protons, while complete reduction of the quinone to the hydroquinone requires two electrons and two protons These protons are in principle available because the reduction is carried out in a methanol/water solution We propose, however, that the reduction of the quinone in this case involves a one electron process that yields the semiquinone The other electron would remain with the rhodium to give a Rh(II) species This second electron is needed later in the reductive activation of dioxygen (see Chapter 2) Once the dioxygen molecule is bound to the Mn(II) metal center, an additional electron (and a proton) is needed to form the Mn(V)-oxo complex

A second reduction, that of Mn(III) to Mn(II) gave rise to a peak at 443 nm The UV-vis spectra of complex **2** and its reduced forms are shown in Figure 4 4

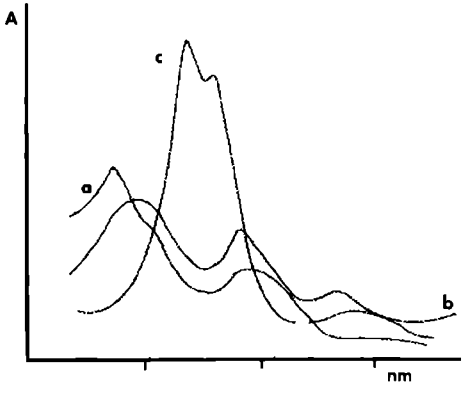
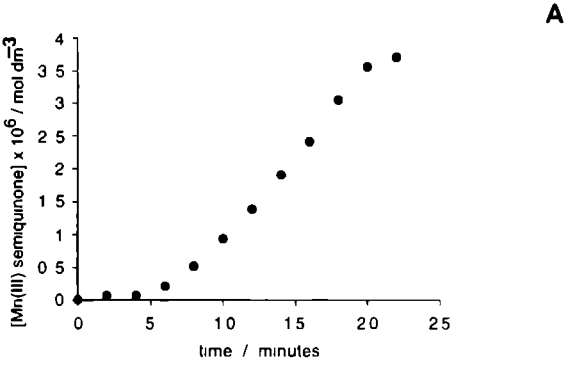


Figure 4.4 *UV-vis spectrum of* **2** *in aqueous methanol solution in the absence (a) and presence of sodium formate after 25 min (b) and 35 min (c) [Complex* **2***] = 2 0 x 10 ^{5} mol dm ^{3}, [sodium formate] = 0 035 mol dm^{-3}, T = 40 4 ^{o}C*

The reaction profiles of these two reductions are shown in Figure 4 5A and B



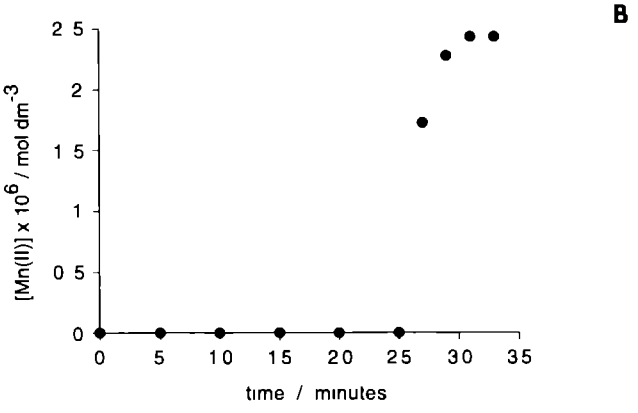


Figure 4.5 *Reduction profile of complex* ***2*** *showing the first reduction (A) which is the reduction of the quinone to the semiquinone and (B) the reduction of Mn(III) to Mn(II) (λ_{max} 443 nm). [Complex 2] = 3.0 x 10^{-5} mol.dm^{-3}, [sodium formate] = 0 035 mol.dm^{-3}, T = 28.6 ^{o}C.*

After an initial induction period of five minutes, the reduction of the quinone to the semiquinone proceeds with zero order kinetics giving a zero order rate constant of (3.90 ± .2) x 10^{-8} mol.dm^{-3}s^{-1}. The reduction of the Mn(III) ion to Mn(II) in complex **2** also followed zero order kinetics with a rate constant of 1.44 ± .07) x 10^{-7} mol.dm^{-3}s^{-1}.

The reduction of complex **1** was further investigated under a variety of conditions. The effect of the amount of sodium formate on the reduction of Mn(III) to Mn(II) is shown in Figure 4.6

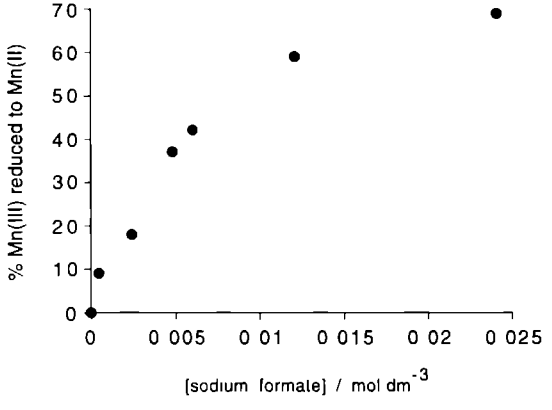


Figure 4.6 *Effect of the concentration of sodium formate on the reduction of Mn(III) to Mn(II) of complex* ***1****. [Complex 1] = 2.0 x 10^{-5} mol.dm^{-3}, T = 40 ^{o}C.*

At low concentrations the amount of Mn(II) formed is proportional to the formate concentration At higher concentrations of formate ion (> 0 015 mol dm^{-3}) the amount of Mn(II) formed levels off (Michaelis-Menten type kinetics) This result is in agreement with the mechanism of rhodium hydride formation proposed by Steckhan and co-workers for the reduction of NAD^+ by formate and Rh(III)bipyCp*Cl [6] That is, the rate determining step of the reaction is the decomposition of the Rh(III)-formate complex that is formed in an equilibrium preceding the rate determining step (See Chapter 3, Scheme 3 4) It is also in agreement with previous work in our laboratory which made use of a Rh(III)bipyCp*Cl complex that was anchored *via* long alkyl chains in a vesicle preparation [4] Experiments with that system also gave Michaelis-Menten type kinetics in the investigation of the effect of the sodium formate concentration on the reduction rate of Mn(III) to Mn(II)

In order to determine the temperature dependence of the reduction of Mn(III) to Mn(II) in complex **1**, we varied the temperature of the reaction and followed the reduction by UV vis absorption spectroscopy The Arrhenius relationship, derived from these data is shown in Figure 4 7 The activation energy was calculated to be 55 ± 4 kJ mol^{-1}

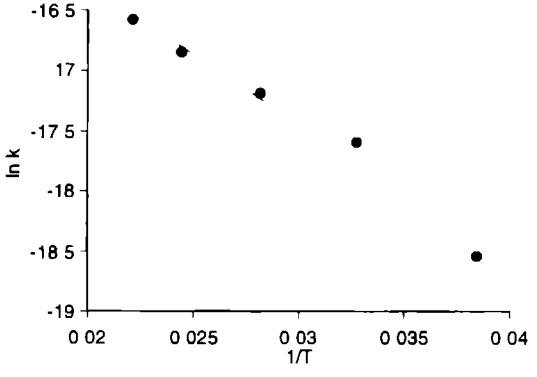


Figure 4.7 *Arrhenius relationship for the reduction of Mn(III) to Mn(II) in complex **1** in methanolic solution [Complex 1] = 2 0 x 10^{-5} mol dm^{-3}, [sodium formate] = 0 035 mol dm^{-3}*

The Eyring plot is given in Figure 4 8 from which the energy parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated These values are 52 6 ± 4 kJ mol^{-1} and -29 0 ±4 J $mol^{-1}K^{-1}$, respectively

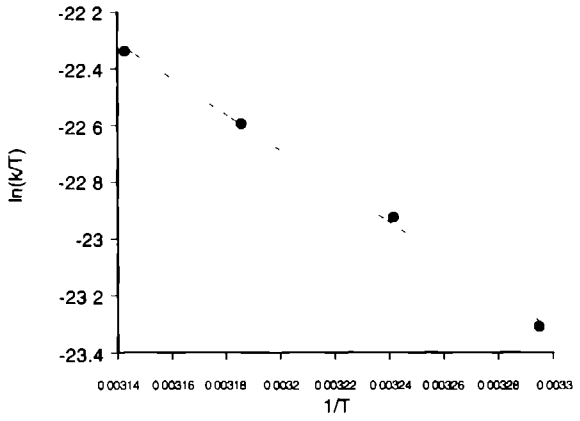


Figure 4.8 *Eyring plot of the reduction of complex **1** with sodium formate.*

Because the rate determining step is the decomposition of the Rh(III)-formate complex to give the rhodium-hydride and CO_2, there is not a great loss in entropy in transition state of the reaction.

Compared with the two-phase system, described in Chapter 3, the pH of the sodium formate solution added to a methanolic solution of complex **1** had little effect on the reduction (Figure 4 9). The reduction proceeded normally except at very low pH (pH 4.2) where the reduction of the Mn(III) ion to Mn(II) did not occur at all. At pH 4.0 in the two-phase system, in contrast, the rate of the reduction was markedly enhanced (see Chapter 3, Figure 3.5).

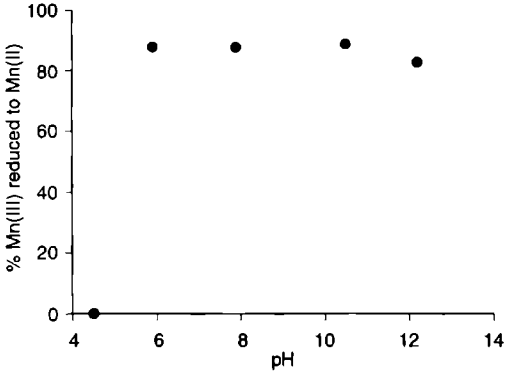


Figure 4.9 *The effect of the pH of the sodium formate solution on the reduction of Mn(III) to Mn(II) in complex **1**; [complex **1**] = 2.0 x 10^{-5} mol.dm^{-3}, [sodium formate] = 0.035 mol.dm^{-3}, T = 40.0 ^{o}C.*

4.2.3 Electrochemistry

The redox properties of complexes **1** and **2** were investigated with cyclic voltammetry in acetonitrile The results are summarized in Table 4 1

Table 4.1 Cyclovoltammetry data from complexes **1** and **2**[a]

Complex	$E_{1/2}$ (V)	ΔEp (mV)	i_b/i_f
1 (without Rh)	-0 41	78	1
1	(1) = 1 20	160	1
	(2) = 0 39	60	
2	$E_{1/2}(1)$ = 1 27	150	1
	$E_{1/2}(2)$ = -0 94		
	E1/2(3) = -0 43	60	96
Mn(III)TPP Cl	-0 65	66	1
Rh(III)bipyCp*Cl	-1 32	250	1 2

[a]Measured in acetonitrile with 0 1 mol dm ^{3} tetrabutylammonium hexafluorophosphate (TBAH) as the supporting electrolyte A three electrode system was used Pt working electrode, Pt auxiliary electrode and a $Ag/AgNO_3$ reference electrode Potentials are reported vs Fc/Fc^{+} in acetonitrile

Complex **2** showed two completely irreversible oxidations and three reductions The first reduction (Rh(III) to (Rh(I)) had a large peak separation which became smaller at slower scan speeds The second reduction (that of the quinone to the semiquinone) became more reversible at higher scan speeds Because the electrochemistry was carried out in acetonitrile, no protons were available, leading us to conclude that the reduction of the quinone with a half wave potential of -0 94 V is a one electron process The half-wave potentials of the third reduction, viz of Mn(III) to Mn(II) (-0 43 V) is comparable, to that observed for complex **1** (-0 39 V) These values represent a positive shift from the half-wave potential of the reduction of Mn(III) to Mn(II) in Mn(III) tetraphenylporphyrin (Mn(III)TPP)) Comparison of the half-wave potentials of complex **1** with and without the coordinated rhodium, shows them to be virtually identical, being -0 39 V and -0 41V, respectively The electrochemical data is in agreement with the UV-vis spectra taken of the reduction of complex **2** by formate In the chemical reduction of **2** by formate, three reductions also occur The first is the reduction of the Rh(III) ion to Rh(I), which from the electrochemistry has the lowest half-wave potential The second reduction is that of the quinone to the semiquinone Since the half-wave potentials of the reductions become more positive in the series Rh(III) < quinone < Mn(III) all of the quinone groups will be first reduced before reduction of the Mn(III) ion occurs This is in line with the results obtained by absorption spectroscopy (see Figure 4 4)

4.2.4 Epoxidation

Epoxidation reactions were carried out with a variety of substrates in $CHCl_3$/methanol/H_2O solution at 40 °C The results are shown in Table 4 2

Table 4.2 Epoxidation results using complexes **1** and **2** as catalysts[a]

Entry	Catalyst	Substrate	Total turnover #
1	**1**	*cis*-Stilbene	227
2	**1**	*trans* Stilbene	102
3	**1**	Limonene	389
4	**2**	*cis*-Stilbene	176
5	**2**	*trans* Stilbene	89
6	**2**	Limonene	320

[a]Reaction conditions 2 0 cm^3 $CHCl_3$, 3 0 cm^3 methanol, 1 4 x 10^{-4} mol dm^{-3} catalyst, 0 5 x 10^{-3} mol dm^{-3} alkene 1 0 cm^3 H_2O 0 050 mol dm^{-3} sodium formate, 1 0 x 10^{-4} mol dm^{-3} *N*-methylimidazole, 0 5 x 10^{-3} mol dm^{-3} benzoic anhydride

Complexes **1** and **2** gave a 10-fold increase in the turnover numbers achieved compared to that of the two-phase system when using comparable substrates such as limonene and α-pinene [8] *Cis*-stilbene and *trans*-stilbene also gave improved yields compared to the two-phase system with *cis*-stilbene giving higher yields of epoxide than the *trans*-isomer due to the steric crowding that occurs in the approach of the *trans*-stilbene molecule to the manganese(V)-oxo center Reactions with cis-stilbene gave exclusively cis-stilbene oxide as product

4.3 Concluding remarks

We were able to show a 10-fold increase in the turnover numbers of epoxide formed using the π-conjugated Mn(III)/Rh(III) complexes **1** and **2** when compared to those of the two-phase epoxidation system described in Chapter 3 After approximately 200-300 catalyst turnovers, however, the reaction stopped in both cases where complex **1** and complex **2** were used as the catalyst The reason why substrate conversion ceased is unclear Analysis of the reaction sample by absorption spectroscopy showed that the catalyst was still intact, even when epoxide was no longer being produced The concentration of the catalyst does decrease by a small amount (10-15%) during the course of the reaction, but this represents a great improvement in stability compared to the Mn(III) porphyrin catalysts in the two-phase system The major difference in using complexes **1** and **2** as catalysts, compared to the two-phase system, is the fact that both the reduction and epoxidation steps occur in a homogenous reaction solution Neither complex **1** nor **2** can be used under two-phase conditions, because the Mn(III) porphyrin part of the molecule cannot be reduced to Mn(II) The Rh(III)-hydride species cannot form when the catalyst (which is only soluble in organic solvents) and sodium formate (soluble

only in aqueous media) are in separate phases While electron transfer from the reduced rhodium atom to the Mn(III) porphyrin is purportedly faster in complexes **1** and **2**, than in the reaction system composed of the Mn(III) porphyrin and Rh(III) bipyridyl complexes as separate components, the lack of separation, i e the separation between the catalyst and the electron source, that was built into the two-phase system has been sacrificed The addition of sodium formate to the homogeneous solution requires that both the reduction of the rhodium ion and the manganese ion occur in the same phase as the epoxidation step Sodium formate is a potential two electron donor and its presence in large excess with complexes **1** and **2** may retard epoxidation of the alkene Work on improving the yields of epoxide in these reactions as well as further investigations into the nature of the electron transfer steps are in progress

4.4 Experimental

Materials. For the reduction experiments and epoxidation reactions, methanol and chloroform were HPLC grade and the water was deionized and doubly distilled Sodium formate was purchased from Aldrich and used as received Alkene substrates were purified by chromatography over basic alumina using dichloromethane as an eluent $Rh(III)Cl_3$ hydrate was purchased from Aldrich and used as received

Instrumentation. IR spectra were taken on a Perkin Elmer 1720-X Infra-red Fourier Transform spectrometer GC-analyses were carried out on a Varian 3700 gas chromatograph with a flame ionization detector, coupled to a Hewlett Packard 3395 integrator The column was a CP-Sil, fused silica column (25 m in length, internal diameter = 25 μ) UV-visible spectra were taken on a Perkin Elmer Lambda 5 spectrometer Mass spectra were taken on a VG 7060 E spectrometer

Syntheses. The manganese(III) / rhodium(III) complex **1** was prepared from the manganese(III) porphyrin bipyridyl ligand* and $[RhCp^*Cl]_2Cl_2$ One half mole equivalent of the $[RhCp^*Cl]_2Cl_2$ was added to a stirring solution of the manganese(III) porphyrin ligand in methanol at room temperature Diethyl ether was added to the reaction mixture to precipitate the product which was filtered and washed with cold diethyl ether to give a dark brown/orange crystalline material UV-vis (methanol, λ_{max} (nm) log (ε / dm^{-3} mol^{-1} cm^{-1})) 484 (3 93), 432 (4 41) FAB-MS *m/z* 1421 $(M - RhCp^*Cl_3)^+$

Complex **2** was prepared from the free ligand * The free ligand (30 mg) was added to refluxing DMF in air To this solution was added (14 mg) Mn(II) acetate tetrahydrate and a ten-fold excess of NaCl After the Mn(III) complex was isolated as a brown powder it was reacted with 0 5 mole equivalents of $[RhCp^*Cl]_2Cl_2$ in methanol at room temperature The solvent was removed and the product dimetallic Mn(III)/Rh(III) complex was isolated as a brown/orange powder
UV-vis (methanol, λ_{max} (nm), log (ε / dm^3 mol^{-1} cm^{-1})) 501 (4 61), 488 (4 52), 383 (4 82) FAB-MS *m/z* 1451 $(M - RhCp^*Cl_3)$

$[RhCp^*Cl]_2Cl_2$ This complex was prepared following a synthesis procedure described by Kang *et al* [9] Rhodium(III) chloride (1 0 g) was added to 10 0 cm^3 of refluxing hexamethyl Dewar benzene The resulting red/brown solution was allowed to reflux in air for 1 h The reaction mixture was allowed to cool and 30 cm^3 of diethylether was added to precipitate the rhodium dimer product The red/brown product was filtered and washed several times with

water, then ether and allowed to dry in air Yield = 88% Physical properties were similar to those reported in the literature

* These ligands were the kind gift of Prof Maxwell Crossley of the University of Sydney, Sydney, Australia

Epoxidation Reactions

A Schlenck tube (10 cm x 2 cm) was charged with 2 0 cm^3 of chloroform, 3 0 cm^3 of methanol, and 1 0 cm^3 of water to give a homogeneous solution To this solution was added the catalyst, alkene, sodium formate, N methylimidazole, and benzoic anhydride to give the following concentrations 1 4 x 10^{-3} mol dm^{-3} catalyst, 0 5 x 10^{-3} mol dm^{-3} alkene, 0 035 mol dm^{-3} sodium formate, 1 0 x 10^{-4} mol dm^{-3} *N*-methylimidazole, and 0 5 x 10^{-3} mol dm^{-3} benzoic anhydride The reaction flask was placed in a thermostatted water bath (40 °C) and stirred vigorously under air The reaction was followed by analyzing an aliquot by GLC

4.5 References

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b Crossley, M J and Burn, P L *J Chem Soc , Commun* **1991**, 1569-1571
c Crossley, M J , Burn, P L , Chew, S S , Cuttance, F B , Newson, I A *J Chem Soc , Chem Commun* **1991**, 1564 1566

2 The ligands for complexes **1** and **2** were prepared in the laboratory of Prof M J Crossley We gratefully acknowledge the gift of these two compounds

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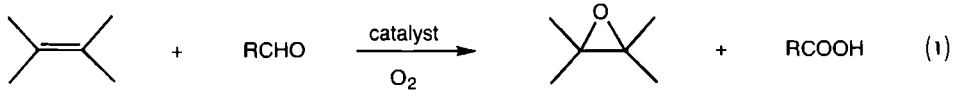
Nickel(II) β-Diketonate Complexes as Catalysts for the Epoxidation of Alkenes by Molecular Oxygen and an Aldehyde: Scope and Limitations

5.1 Introduction

In Chapters 3 and 4, a catalytic system based on a manganese(III) porphyrin and rhodium(III) bipyridyl redox couple that is capable of the reductive activation of dioxygen was described. This process involves the binding of an oxygen molecule to the reduced metal center of the catalyst, reduction of the metal-oxo species, splitting of the dioxygen bond and insertion of the "activated" oxygen atom into an appropriate alkene substrate.[1-3] In this chapter, we describe a catalytic system that catalyzes the epoxidation of unfunctionalized alkenes by a nickel(II) β-diketone catalyst in the presence of molecular oxygen and an aldehyde as co-reductant. This reaction is illustrated by equation (1)



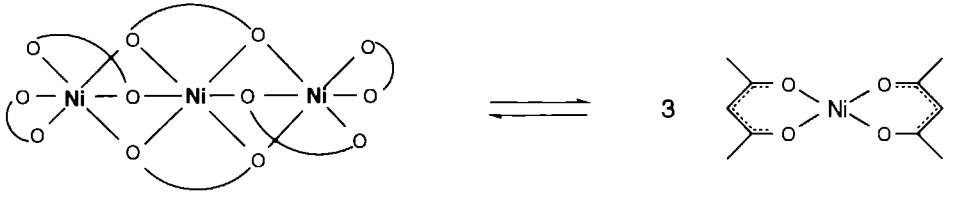
(1)

While nickel has been widely used industrially as a catalyst for a number of reactions,[4,5] including the partial oxidation of methane,[6] ethylene dimerization,[7] alkene synthesis from syngas,[8] and the hydrogenation of vegetable oils,[9] its use as a homogeneous catalyst in the epoxidation of alkenes has been described in only a few cases, namely with tetraaza macrocycles as ligands with NaOCl or iodosylbenzene as the terminal oxidant,[10-14] and most recently with acetylacetonate-type ligands complexed to nickel(II) as described in investigations by Mukaiyama and co-workers [15,16] We wanted to explore the scope and efficacy of a variety of β-diketonate ligands that, when complexed to a nickel(II) ion, can act as catalysts for reaction (1). The results are described here.

5.1.2 Nickel(II) complexes of pentane-2,4-dione and its 3-substituted derivatives

Nickel(II) chelates of β-diketonate ligands have been intensely investigated,[17-28] not, until recently, for their catalytic abilities, but for their unusual electronic properties [23,26,28] Anhydrous nickel(II) acetylacetonate (abbr. Ni(II)acac$_2$), a Lewis acid, is bright emerald green in color and is paramagnetic in the solid state (μ = 3.27 B M. at 27°).[28] Similar paramagnetic

moments have been measured in benzene, chloroform, and methanol solutions.[28] The anhydrous complex readily forms a dihydrate which is aqua in color. The difference in color between the anhydrous and the dihydrate complexes is easily seen with the eye, but the absorption spectra of the two complexes are virtually identical [29] Although originally thought to be tetrahedral, it was shown that the structure of Ni(II)acac$_2$ in non-coordinating solvents and in the solid state is actually a trimer with six oxygen atoms arranged around each nickel atom in an approximately octahedral arrangement.[19] This trimeric species is in equilibrium with the monomeric conformer (Scheme 5.1). This associated structure leads to ferromagnetic interaction of the nickel atoms at low temperatures.[19]



Scheme 5.1 *Schematic drawing of the structure of the Ni(II)acac$_2$ trimer and its square planar monomer*

Substituted pentane-2,4-dione nickel-(II) complexes exhibit only partial association in solution depending upon the degree of steric hindrance and the nature of the electronic character of the substituents.[18,20,24,26,28] Trimeric association of these complexes is also dependent upon other factors, including temperature and concentration.[26,27,28] Fully hindered complexes such as bis-(dipivaloylmethano)-nickel(II) exist in noncoordinating solvents only in the monomeric, diamagnetic state, while bis-(trifluoroacetylacetonato)-nickel(II) occurs only in the paramagnetic trimer configuration.[28] The low-spin forms are red/purple in color with an absorption at 520 nm in the visible spectrum (ε = 53) appearing on the tail of a high intensity absorption band in the ultra-violet region.[28] The square-planar structure of these complexes has been determined by x-ray analysis.[19] The equilibrium between the low-spin and high-spin forms is dependent upon the donor strength of the ligand, expressed as p_{Ka}, and, to a lesser extent upon steric hindrance.[20,24,26]

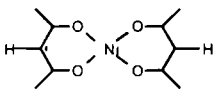
Because many epoxidation catalysts rely on a square planar configuration of the metal ion to facilitate oxygen atom transfer to the alkene,[30] we became interested in investigating the catalytic properties of substituted Ni(II)acac$_2$ complexes to determine the relationship between the steric and electronic properties of the catalyst and catalytic activity

5.2 Results and discussion

5.2.1 Catalyst stability

Complexes **1** **8** shown in Chart 5 1 were prepared following standard procedures and used as catalysts for reaction (1)

Chart 5.1



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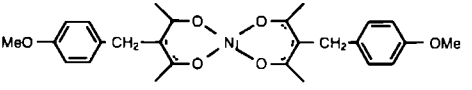

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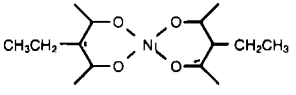

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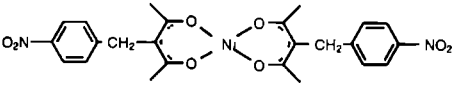

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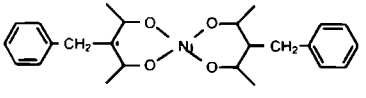

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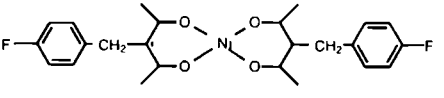

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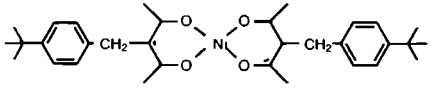

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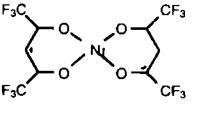


8

During a typical reaction run using the standard conditions described in Section 5 4, the catalyst (complex **4**) remained relatively intact as long as there was sufficient substrate available in the reaction mixture After 100% substrate conversion, or in the complete absence of alkene (in this case α pinene) the catalyst was rapidly degraded (Figure 5 1)

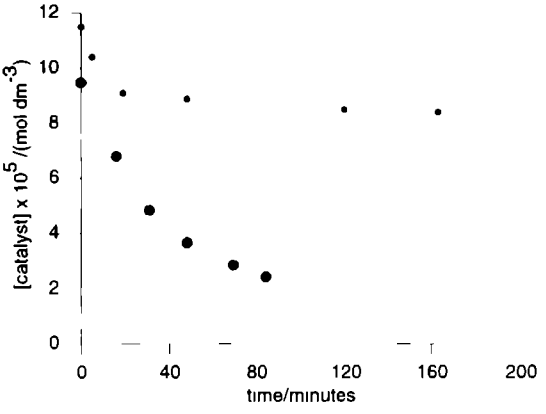


Figure 5.1 *Stability of complex **4** in the presence (•) and absence (•) of substrate (α-pinene) Standard conditions*

Metal acetylacetonates are known to be subject to oxidative degradation by attack at the carbon-3 position of the ligand It has been shown, however, that substitution at the 3-position with either phenyl or benzyl groups (as in our case) greatly increases the stability of the acetylacetonate ligands to oxidative degradation [31] Nevertheless, it is clear that oxidative degradation of the catalyst is a competing side reaction under the conditions we used for the epoxidation of alkene substrates High selectivities and high yields of epoxide are only likely to be obtained with reactive substrates An unreactive substrate will not be able to compete successfully for reaction with the active oxidizing species and degradation of the catalyst will occur at a more rapid rate than conversion of the alkene to epoxide This conclusion is evident when examining the reactivity of a variety of alkenes and the yield of epoxide that is produced during a standard reaction run (see below)

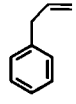
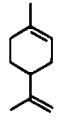
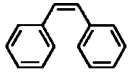
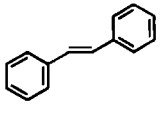
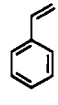
5.2.2 Reaction scope

To determine the scope of the reaction, epoxidation reactions were carried out with a variety of substrates, aldehydes, and catalysts, including other (non-nickel) metal-β-diketonates such as $Mn(II)acac_2$, $Co(II)acac_2$, and $Fe(III)acac_2$, and nickel(II) catalysts based on the macrocyclic ligand systems of salen and porphyrin

Reactivity of alkenes

Epoxidation reactions were carried out using standard conditions and complex **4** as the catalyst. A variety of non-functionalized alkenes were employed as substrates. The results are shown in Table 5.1.

Table 5.1 Epoxidation results with various unfunctionalized alkenes using complex 4 as catalyst[a]

Substrate	% Conversion	% Yield epoxide	Substrate	% Conversion	% Yield epoxide
	93	86		51	47
	27	23		16	12
	77	72		41	36
	100	96		6	5
	68	61		49	45
	9	6		23	19

[a]Reaction conditions. 0.1 mol.dm^{-3} alkene, 0.3 mol dm^{-3} isobutyraldehyde, 1.0 x 10^{-3} mol dm^{-3} catalyst **4**, 5.0 cm^3 CH_2Cl_2, 1.0 atm O_2, 25° C

Triply substituted alkenes such as α-pinene and limonene gave very good yields (86% and 72% respectively) of epoxides under the standard reaction conditions. Doubly substituted and electron-rich alkenes such as *cis*-stilbene, cyclohexene, β-pinene, *trans*-β-methylstyrene and camphene gave poorer, but still respectable yields of epoxides ranging from 23% for β-pinene to 61% for camphene. The outstanding exception is norbornene, a doubly substituted alkene which gave 96% epoxide. Furthermore, the selectivity for epoxidation of these substrates was very high (>95%) with only trace amounts of by-products formed. These by-products were isomers of the starting alkene formed most likely by rearrangement of the carbon skeleton. The least reactive substrates appeared to be electron-rich alkenes that are singly substituted,

including styrene, octene, and allyl benzene. *Trans*-stilbene, an electron-rich, doubly substituted alkene gave very poor yields of epoxide, averaging 5%.

Reactivity of aldehydes

The reactivity of various aldehydes as co-reductants was examined in epoxidation reactions that used α-pinene as substrate and complex **4** as catalyst under standard conditions. The results are shown in Table 5.2.

Table 5.2 Epoxidation results with α-pinene and various aldehydes catalyzed by complex **4**[a]

Aldehyde	% Yield α-pinene epoxide
Isobutyraldehyde	81
Butyraldehyde	5
Acetaldehyde[b]	2
Propionaldehyde	2
Benzaldehyde	0
Cinnamaldehyde	0
Pivaldehyde	68
Crotonaldehyde	0

[a]Reaction conditions 0.1 mol dm^{-3} alkene, 0.3 mol dm^{-3} aldehyde, 1.0 x 10^{-3} mol dm^{-3} catalyst **4**, 5.0 cm^3 CH_2Cl_2, 1.0 atm O_2, 25° C

[b]due to its low boiling point, the reaction with acetaldehyde was carried out at 15 °C

The recent work of Mukaiyama and co-workers,[15,16] who published the initial reports on the epoxidation of alkenes in the presence of nickel catalysts and aldehyde/O_2 have suggested that the aldehyde acts as a reductant, e.g. the aldehyde accepts the second oxygen atom that is cleaved from the purported nickel-oxo active species. These reports suggested no mechanism for this process, but their explanation of the aldehyde accepting the other oxygen atom from molecular oxygen after it is bound to the nickel seems unlikely in view of the large difference in aldehyde reactivities. More detailed information about the mechanism we have proposed for this reaction sequence is given in Chapter 6 of this thesis

It is clear from the results in Table 5.3, however, that only aliphatic branched aldehydes, such as isobutyraldehyde and pivaldehyde, are active as co-reductants, while aromatic or π-conjugated aldehydes, such as benzaldehyde, cinnamaldehyde, and crotonaldehyde, are weakly or completely inactive.

5.2.3 Electronic and steric effects of substituted pentane-2,4-dione nickel(II) complexes

Because variation of the electronic nature of the ligand can lead to changes in the epoxidation rate of the catalyst--by either affording greater stability to the ligand or by stabilizing the intermediate responsible for oxygen transfer--we studied the effect of substitution at the 3-position of the acetylacetonate group with different alkyl groups and the effect of different

substituents at the para-position of the 3-benzyl group. The ability of the catalysts to convert α-pinene to its corresponding epoxide was investigated under the standard set of reaction conditions. The results are listed in Table 5.3.

Table 5.3 Epoxidation of α-pinene with various substituted β-diketonate nickel(II) complexes[a]

Catalyst	Substituent at the 3-position	Turnover #/h
1	H	15
2	ethyl	8
3	benzyl	11
4	*p*-*t*-butyl benzyl	21
5	*p*-MeO-benzyl	32
6	*p*-NO_2-benzyl	39
7	*p*-F-benzyl	24
8	H, (1,5-CF_3)	1

[a]Reaction conditions 0.1 mol dm^{-3} α-pinene, 0.3 mol dm^{-3} isobutyraldehyde, 1.0 x 10^{-3} mol dm^{-3} catalyst, 5.0 cm^3 CH_2Cl_2, 1.0 atm O_2, 25° C. Reaction time = 6 h.

The data in Table 5.1 reveal several interesting points. First, the efficency of the catalyst is not significantly enhanced by replacing the H-atom at the 3-position with an alkyl group such as an ethyl or benzyl group (catalysts **2**,**3**). The catalyst efficiency is significantly enhanced, however, by modifying the 3-position with a para-substituted aromatic group (catalysts **4**-**7**). We found some difference, however, in the results using catalysts **4**-**7** where the benzene ring is modified with either electron-withdrawing or donating groups. In addition to its electron-withdrawing effect, catalyst **6**, modified with a NO_2 group may have a stabilizing effect, as it gives 39 turnovers per hour as opposed to the *t*-butyl benzyl sustituted complex **4** which gives 21 turnovers per hour.

5.2.4 Comparative reactivity of various transition metal complexes and transition metal salts

Because the nickel(II) acetylacetonate catalysts appeared to be quite efficient at converting alkenes to their corresponding epoxides, we were interested in whether or not other nickel-containing complexes were active as catalysts. Therefore, several transition metal complexes with salen or porphyrin ligands were investigated for their catalytic activity in the conversion of α-pinene to α-pinene epoxide. Several transition metal salts were also studied for their catalytic activity. The results are shown in Table 5.4.

Table 5.4 Epoxidation results with α-pinene and a variety of transition metal catalysts[a]

Catalyst	% Conversion	% Yield epoxide	Selectivity
$Ni(II)OAc_2$	80	63	79
$Co(II)OAc_2$	100	87	87
$Mn(II)OAc_2$	48	37	77
$Fe(III)OAc_2$	31	0	0
$Ni(II)acac_2$	100	91	91
$Co(II)acac_2$	0	0	0
$Mn(II)acac_2$	99	61	62
$Fe(III)acac_3$	25	22	88
$Pd(II)acac_2$	<1	<1	-
Ni(II)salophen	53	43	89
Co(II)salophen	0	0	-
Mn(III)salophen	36	6	17
Fe(III)salophen	21	13	62
Ni(II)TPP	100	61	61
Co(II)TPP	nd[b]		
Mn(III)TPP	99	78	79
Fe(III)TPP	0	0	-

[a]Reaction conditions 0 1 mol dm ^{3} α pinene, 0 3 mol dm ^{3} isobutyraldehyde, 1 0 x 10^{-3} mol dm ^{3} catalyst, 5 0 cm^{3} CH_2Cl_2, 1 0 atm O_2, 25° C Reaction time = 6 h

[b]not determined

Remarkably, the metal salts $Ni(II)OAc_2$ and $Co(II)OAc_2$ were almost as efficient at converting α-pinene to its epoxide as was $Ni(II)acac_2$, although the selectivity for epoxide was somewhat lower, being 79% and 87%, respectively, while the selectivity of $Ni(II)acac_2$ for epoxide was 91%. $Mn(II)OAc_2$ gave a relatively high selectivity (77%), but a low yield of epoxide (37%) after which time, substrate conversion ceased $Fe(III)OAc_2$ converted 31% of α-pinene to oxidation products, but no epoxide was formed Although the products were not identified in this reaction, they are most likely a result of Fenton-type chemistry Of the metal-acetylacetonates used as catalysts, only $Ni(II)acac_2$ gave satisfactory epoxide yields and selectivities $Mn(II)acac_2$ was able to convert 99% of the starting alkene, but produced only 61% epoxide, with the products being contaminated by a variety of oxidation products The $Fe(III)acac_3$ gave an excellent selectivity for epoxide but a low yield in the prescribed reaction time Surprisingly, $Pd(II)acac_2$ and $Co(II)acac_2$ gave no epoxide yield and were both completely unreactive at converting substrate to any oxidation products At higher concentrations (3 mol % respective to the alkene), $Co(II)acac_2$ was able to convert α-pinene to

epoxide Thus it is not possible to conclude that catalyst reactivity under these conditions can be generalized to all group eight metals

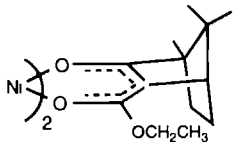
The other metal containing catalysts with more extensive ligand systems (the salophens and porphyrins) gave varied results Ni(II)salophen afforded a high selectivity, but low yield The dark red color of the solution that was due to the dissolved catalyst also diminished in color to a pale orange during the reaction, indicating the oxidative degradation of the ligand Ni(II)TPP, in contrast, was able to convert 100% of the alkene, but epoxide yield and selectivity were low (61%) Mn(II)salophen afforded epoxide in low yields with a large number of oxidation by-products Fe(III)salophen gave a mixture of oxidation products with the selectivity for epoxide being 62%, while Fe(III)TPP gave no products Co(II)salophen, like Co(II)$acac_2$ was completely inactive at 1 mole % catalyst, but Mn(III)TPP appeared to be a fairly good catalyst with 99% substrate conversion and 79% selectivity for epoxide

5.2.5 Solvent effects

Coordinating solvents could potentially poison the catalyst by binding to free sites on the nickel atom, preventing binding of the aldehyde (see Chapter 6) Therefore, we investigated the effect of the various solvents on the rate of the reaction The reaction ran fastest in dichloromethane with a slightly slower rate in acetonitrile, which is a partially coordinating solvent The order in rate of other solvents was as follows toluene > tetrahydrofuran > acetone The reaction did not occur at all in DMF or in ethanol which is consistent with the expectation that coordinating solvents would inhibit the reaction by blocking access of the aldehyde to binding on the nickel atom of the catalyst For additional details, see Chapter 6, Figure 6 12

5.2.6 Chiral nickel(II) β-diketonate catalysts

As discussed in Chapter 2, the oxidation of alkenes to their corresponding epoxides provides a possible means of introducing either one or two chiral centers in the carbon skeleton Enantioselective control of the products is important in the pharmaceutical industry as well as in the synthesis of natural products [32] We were interested in investigating the asymmetric induction capabilites of some chiral nickel(II) β diketonates to determine whether enantioselective epoxidation could be achieved In an analogous reaction described in the literature[33], *i e* the cyclopropanation of alkenes, high enantioselectivities were achieved with chiral cobalt(II) β diketonate catalysts in which the ligands were derived from simple molecules from the chiral pool The chiral complexes shown in Chart 5 2 were used as potential enantioselective catalysts



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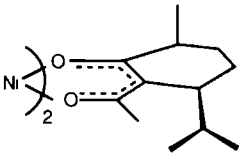

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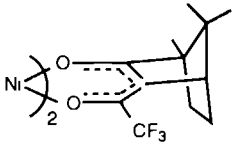

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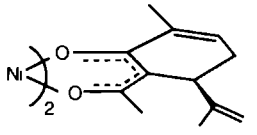

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Epoxidation

Epoxidation reactions using complexes **9-12** were carried out with *trans*-stilbene and *trans*-β-methyl styrene. No ee's were found in the product epoxides (Table 5 5). This may be a result of the lability of the β-diketonate ligands, which would preclude a rigid transition state, or because of a radical species that forms during oxygen transfer. The proposed mechanism of this reaction is discussed in detail in Chapter 6.

Table 5.5 Epoxidation results with chiral nickel(II) β-diketonate catalysts[a]

Entry	Catalyst	Substrate	% Yield epoxide	% e.e.
1	**9**	*trans*-Stilbene	4	0
2	**9**	*trans*-β-Methylstyrene	43	<1
3	**10**	*trans*-Stilbene	2	0
4	**10**	*trans*-β-Methylstyrene	14	<1
5	**11**	*trans*-Stilbene	6	0
6	**11**	*trans*-β-Methylstyrene	39	0
7	**12**	*trans*-Stilbene	5	0
8	**12**	*trans*-β-Methylstyrene	46	<1

[a]Reaction conditions 5 0 x 10^{-3} mol dm^3 alkene, 1 5 x 10^{-3} mol dm^3 isobutyraldehyde, 1 0 mole % catalyst, 5 0 cm^3 dichloromethane, 25° C Reaction time = 4 hrs

5.3 Concluding remarks

Inspired by the initial reports of Mukaiyama and co-workers concerning the ability of Ni(II) β-diketonate type catalysts to epoxidize alkenes in the presence of molecular oxygen and an aldehyde, we were interested in exploring the scope of these reactions as well as to determine

the activity of related nickel, and other transition metal catalysts. We have shown that in the presence of a branched aliphatic aldehyde, such as isobutyraldehyde or pivaldehyde, nickel(II) β-diketonate complexes are efficient and highly selective catalysts for the epoxidation of unfunctionalized alkenes. Certain types of alkenes, such as those that are triply substituted, including terpenes such as α-pinene and limonene, are particularly reactive substrates under these reaction conditions. Doubly substituted alkenes such as camphene and norbornene also gave high epoxide yields. In contrast to other epoxidation reaction conditions[10-14] that use oxidants such as iodosylbenzene or NaOCl, electron-rich alkenes including *cis*- and *trans*-stilbene and styrene were less reactive.

While several other transition metals and other metal-ligand combinations were shown to be active catalysts in the epoxidation of alkenes by oxygen in the presence of isobutyraldehyde, including Ni(II)TPP, Mn(III)TPP, and Mn(II)$acac_2$, these complexes, while often capable of completely converting the substrate, had typically much lower selectivities in terms of converting alkene to epoxide. Interestingly, several transition metals salts were also quite efficient in converting alkene to epoxide, including Co(II)OAc_2, which when complexed to acetylacetonate, salen or porphyrin ligands was inactive as a catalyst. This lack of activity is probably due to the fact that Co(II) is particularly susceptible to aerial oxidation when it is complexed to various ligands [17]

Ni(II) acetate, Ni(II) propionate, and Ni(II) benzoate also proved to be excellent catalysts under the standard reaction conditions, although their solubilities in most non-polar organic solvents is quite poor. Interestingly a nickel salt with a non-coordinating anion such as Ni(II) tetraborohydrate was not active as a catalyst when the reaction was run in acetonitrile (results not shown). Clearly the central nickel atom must be stablized by some coordinating ligands or anions for the active oxidizing species to be formed and the reaction to proceed. Of the 3-substituted β-diketonate nickel(II) catalysts, complexes **5** and **6** gave the highest yields. This is more likely due to the higher stability of these complexes than to the electronic effects of the para-substituents The stability of the catalyst is an important factor in the eventual epoxide yield because degradation of the catalyst is a competing side reaction. In the absence of an alkene substrate, the catalyst itself is rapidly degraded. As long as there is sufficient (reactive) alkene present in the reaction mixture, the catalysts remained intact. With the less reactive substrates such as *cis*- and *trans*-stilbene, the catalyst was degraded before all of the substrate is able to be converted to epoxide. Substitution at the 3-position, however, markedly increased the turnover rate of the epoxide formed when comparing compounds such as **4**-**6** with non-substituted Ni(II) acetylacetonate. The presence of several electron-withdrawing groups on the ligand such as in complex **8** with its 18 fluorine atoms appeared to greatly decrease the efficiency of the catalyst, probably by destablizing the putative nickel-peroxo species that is the likely oxygen atom transfer agent

We showed that it is possible to inhibit the reaction by poisoning the catalyst with coordinating solvents such as DMF and EtOH. It is necessary for the aldehyde to coordinate to the vacant sites on the nickel(II) atom for the epoxidation reaction to take place Therefore, only non-coordinating solvents such as dichloromethane and toluene are suitable for the reaction, or a weakly coordinating solvent such as acetonitrile, which gave a similar rate of reaction as that in dichloromethane. Other weakly coordinating solvents such as tetrahydrofuran and acetone, decreased the rate of the formation of epoxide, but did not inhibit the conversion of substrate.

More about the proposed mechanism of the formation of the active oxygen species is discussed in Chapter 6.

Chiral nickel(II) β-diketonate complexes based on readily available and easily modified compounds from the chiral pool, such as camphor, menthone, and carvone did not show asymmetric induction in epoxidation reactions with *trans*-stilbene, and *trans*-β-methyl styrene as substrates. This lack of inducible asymmetry can be attributed to the lability of the β-diketonate ligands, preventing the formation of a rigid, chiral transition state, and to the likely radical nature of the oxygen transfer process which allows for rotation around the double bond of this substrate. This process is explained in more detail in Chapter 6 where in-depth mechanistic studies are described.

5.4 Experimental

Materials. Pentane-2,4-dione was purchased from Aldrich and distilled before use. Ethyl bromide, benzyl bromide, *p*-nitrobenzylbromide, *p*-methoxybenzylbromide, *p*-fluorobenzylbromide and *p*-*t*-butylbenzyl chloride were purchased from Aldrich and used without further purification. For the chiral complexes, (**1***R*)-(+)-camphor, (-)-menthone, and (*R*)-(-)-carvone were purchased from Aldrich and used without further purification. Acetyl chloride and diethylcarbonate were distilled before use (+)-3-(Trifluoroacetyl)camphor was used as received. All alkene substrates were commercial samples and were purified by column chromatography over basic alumina with dichloromethane as eleunt. Their corresponding epoxides were either purchased from Aldrich or prepared by epoxidation of the alkene with *m*-CPBA in dichloromethane.

Instrumentation. UV-vis spectra were taken on a Perkin-Elmer Lambda 5 spectrophotometer Gas chromatography was performed on a Varian 3700 equipped with a flame-ionization detector and coupled to a Hewlett Packard 3395 integrator. (Column: fused silica capillary column, CP-sil, 25 m, 25 μm diameter). The enantioselective excess (ee) of product epoxides was determined with HPLC using a chiral solid phase column (Chiralpak OD or AD) with a LKB Bromma 2150 HPLC ramp and a 2152 HPLC controller, coupled to a LKB Bromma 2221 integrator. Elemental analyses were determined with a Carlo Erba EA 1108. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected.

Syntheses

Nickel(II) acetylacetonate was prepared as follows. 0.5 g (2 0 mmol) nickel (II) acetate tetrahydrate dissolved in 2.0 cm^3 water was added to a stirring solution of 0.6 cm^3 (6.0 mmol) pentane-2,4-dione in 15 cm^3 ethanol. A small amount (~ 1 0 cm^3) of aqueous 25% ammonium solution was added to deprotonate the acetylacetonate molecule at the 3-position and to facilitate complexation. Water was added to precipitate the product which was subsequently filtered and washed with water and then ethanol to give the aqua colored Ni(II)$acac_2$.$(H_2O)_2$ in 94% yield Anhydrous Ni(II)$acac_2$ was obtained by azeotropic distillation in toluene to give a pale green powder. Co(II)$acac_2$, Fe(III)$acac_2$ Pd(II)$acac_2$ and Mn(II)$acac_2$ were prepared from pentane-2,4-dione and the appropriate metal salt in an analogous manner. The physical properties of the complexes were similar to literature values.[34]

3-substituted pentane-2,4-dione ligands. These compounds were prepared according to a modified literature procedure.[35] To a suspension of 13.5 g K_2CO_3 in dry acetone (100 cm^3)

cm^3) was added 5 0 cm^3 (0 05 mol) pentane 2,4-dione and 0 06 moles of the appropriate alkyl halogen The mixture was stirred and allowed to relux in air for 4 hours The reaction mixture was cooled to room temperature and then placed in an ice bath Petroleum ether was added (30 cm^3) and the inorganic salts were filtered off The filtrate was washed with petroleum ether and acetone and the fractions were collected The solvents were removed to yield a mixture of product and unreacted pentane-2,4-dione In the cases where the product was liquid, the remaining pentane-2,4-dione was distilled off and the product β-diketone was further purified by distillation In the cases where the product β-diketone was solid, it was filtered to remove any remaining pentane 2,4-dione, washed and purified by re-crystallization

Nickel(II) β-diketonate catalysts. Nickel(II) complexes of the ligands were prepared by dissolving 3 0 mole equivalents of the the β-diketonate ligand in ethanol and adding 1 0 mole equivalent of $Ni(II)OAc_2$ dissolved in ethanol A small amount (~1 0 cm^3) of 25% ammonia solution was added to the reaction mixture to deprotonate the ligand at the 3-position and to facilitate complexation The reaction mixture was stirred at room temperature for 2 hrs, during which time the product precipitated from the solution The product was further precipitated by the addition of water, filtered and washed with water, cold ethanol and dried in air, to give the dihydrated product To obtain the anhydrous complexes that were used for all epoxidation reactions, the hydrated complexes were dried by the azeotropic distillation of toluene, after which they were washed with dry hexane and dried under high vacuum

Synthesis of salen and porphyrin complexes. The transition metalcomplexes of salen and porphyrin ligands were prepared using standard literature procedures[36] and their physical properties were compared with the literature values

3-Ethyl-2,4-pentanedione

Yield 47% of a pale yellow oil ^{1}H-NMR ($CDCl_3$) δ 15 76 (s, 1H, enol OH), 3 46-3 10 (q, 2H, CH_2), 2 12-2 98 (t, 3H, CH_3), 2 01, 1 96 (2s, 6H, CH_3)

Bis-(3-ethyl-2,4-pentanediono)-nickel(II), 2

Yield 76% of a pale purple powder IR (KBr) ν_{max} (cm^{-1}) 1558, 1469, 1357 (C O)
Anal calc for $C_{14}H_{22}O_4Ni\ 2H_2O$, C 48 15, H 7 51, found C, 47 65, H 6 92

3-Benzyl-2,4-pentanedione

Yield 53% of cream colored crystals ^{1}H NMR ($CDCl_3$) δ 16 84 (s, 1H, enol OH), 7 36 - 7 10 (m, 5H, ArH), 3 65 (s, 2H, benzyl CH_2), 2 12, 2 06 (s 6H, CH3) M p = 224-226 °C

Bis-(3-benzyl-2,4-pentanediono)-nickel(II), 3

Yield 83% of a pale green powder IR (KBr) ν_{max} (cm^{-1}) 1560, 1471, 1360 (C-O)
Anal calc for $C_{24}H_{26}O_4Ni\ 2H_2O$, C 60 92, H 6 39, found C 58 65, H 5 75 M p decomposes at 264 °C

3-(*p-t*-Butylbenzyl)-2,4-pentanedione

Yield 56% cream colored crystals ^{1}H-NMR ($CDCl_3$) δ 16 82 (s,1H, enol OH), 7 28 6 90 (m, 4H, ArH), 3 22 (s, 2H, benzyl CH_2), 2 14 (s), 2 09 (s), 1 26 (s), (9H, *t* butyl CH_3) M p = 137 °C

Bis-[3-(*p-t*-butylbenzyl)-2,4-pentanediono]-nickel(II), 4

Yield 87% purple crystalline solid IR (KBr) ν_{max} (cm^{-1}) 1561, 1471, 1362 (C-O)

Anal calc. for: $C_{32}H_{42}O_4Ni$; C 69.96, H 7.71; found: C 70.14, H 7.65. M.p > 400 °C

3-(*p*-Methoxybenzyl)-2,4-pentanedione

Yield 54% of a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.42-6.72 (m, ArH), 3.76 (s, 2H, benzyl CH_2), 2.10 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). M.p = 113 °C.

Bis-[3-(*p*-methoxybenzyl)-2,4-pentanedionato]-nickel(II), 5

Yield 89% brown cystalline solid. IR (KBr) ν_{max} (cm^{-1}). 1560, 1378, 1367 (C-O).
Anal. calc. for: $C_{26}H_{30}O_6Ni\ H_2O\ NH_3$, C 58 67, H 6.63, N 2.63; found: C 63.47, H 6.46, N 1.16.

3-(*p*-Nitrobenzyl)-2,4-pentanedione

Yield 33% yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 16.87 (s, 1H, enol OH), 8.23-8.14 (m, ArH), 7.37-7.26 (m, ArH), 3.77 (s, 2H, benzyl CH_2) 2.07 (s, 6H, CH_3). M.p. = 186 °C.

Bis-[3-(*p*-nitrobenzyl)-2,4-pentanedionato]-nickel(II), 6

Yield 74% yellow powder. IR (KBr) ν_{max} (cm^{-1}): 1564, 1502, 1375, 1310 (C-O)
Anal. Calc. for· $C_{24}H_{24}N_2O_8Ni\ NH_3\ H_2O$; C 51.27, H 5.20, N 7 47; found: C 50.28, H 5.24, N 8 17. M.p. > 400 °C.

3-(*p*-Fluorobenzyl)-2,4-pentanedione

Yield 72% of a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 16.64 (s, 1H, enol OH), 7 21-6.85 (m, ArH), 2.13, (s), 2.09 (s).

Bis-[3-(*p*-fluorobenzyl)-2,4-pentanedionato]-nickel(II), 7

Yield 65% of a brown powder. IR (KBr) ν_{max} (cm^{-1}): 1567, 1382, 1369 (C-O); 638 (C-F)
Anal. Calc for· $C_{24}H_{24}O_4F_2Ni\ 2NH_3$, C 56 72 H 5 25 N 2.76 found: C 56.67 H 4.99 N 3 33 M.p. > 400 °C.

Bis-(1,5-trifluoro-2,4-pentanedionato)-nickel(II), 8

Yield 93% of a pale green powder. IR (KBr): 1248, 1187, 1125 (C-O), 798, 630, 589 (C-F)
Anal. Calc. for $C_{10}F_{12}O_4Ni.2NH_3$, C 23.79, H 1.20, N 5 55 found C 23 65, H 1 70, N 5 26 M.p. = decomposes at 360 °C

Synthesis of chiral β-diketonate Ni(II) catalysts, 9-12. Catalysts **9**, **10**, and **12** were prepared using a modified literature procedure.[36] 1.0 g of the appropriate substrate, (**1***R*)-(+)-camphor, (-)-menthone, or (*R*)-(-)-carvone was treated with 2.0 mole equivalents of K-*t*-butoxide in refluxing toluene. To this mixture was added 1.0 mole equivalent of acetyl chloride (in the case of camphor, diethylcarbonate was used as the acylating agent). The reaction was refluxed for 1 h, or until TLC showed that the reaction was complete. The mixture was allowed to cool andwas poured onto ice that was acidified with a aqueous solution of 10% HCL. The organic layer was separated and washed twice with a 5% sodium bicarbonate solution and then with water. The solvent was removed to yield the products as yellow oils. The corresponding nickel(II) complexes were prepared in the manner described above for the 3-substituted pentane-2,4-dione complexes

3-(Acetylethylester)camphor

Yield 23% of a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 12 11 (s, 1H, enol OH), 4.31-4 09 (q, 5H, -CH_2CH_3, J = 7 Hz) 3 46 (s, 2H, benzyl CH_2) 2.27 (s), 0 96, 0.91, 0.83 (3 s, 9H, CH_3)

Bis-(3-acetylethylestercamphorato)-nickel(II), 9

Yield 80% of a pale green powder IR (KBr) ν_{max} (cm ^{1}) 1741, 1262 (C-O)
Anal Calc for $C_{26}H_{38}O_6Ni\,2H_2O$, C 57 69, H 7 82 found C 56 27, H 8 04
M p > 400 °C

Bis-(3-trifluoroacetylcamphorato)-nickel(II), 10
Yield 96% yield of a pale green powder IR (KBr) ν_{max} (cm-1) 1722, 1253 (C-O), 732
Anal Calc for $C_{24}H_{28}O_4F_6Ni$, C 52 11, H 5 10 found C 51 98, H 4 57 M p > 400 °C

3-(Acetyl)carvone
Yield 58% of a colorless oil ^{1}H NMR ($CDCl_3$) δ 12 60 (s, 1H, enol OH), 2 39 (s), 2 28 (s) 2 24, 1 31, 1 24 (2 s, 6H, CH_3)
Bis-(3-acetylcarvonato)-nickel(II), 11
Yield 77% of a pale green/brown powder IR (KBr) ν_{max} (cm ^{1}) 1417, 1378, 1261 (C-O)
Anal Calc $C_{24}H_{30}O_4Ni$, C 65 34, H 6 85 found C 64 50, H 6 84 M p > 400 °C

3-(Acetyl)menthone
Yield 43% of a colorless oil ^{1}H NMR ($CDCl_3$) δ 16 74 (s, 1H, enol OH), 2 05 (s, CH_3), 0 85, 0 79, 0 73 (3 s, 9H, CH_3)
Bis-(3-acetylmenthonato)-nickel(II), 12
Yield 83% of a pale green powder IR (KBr) ν_{max} (cm ^{1}) 1622, 1422, 1380, 1261 (C-O)
Anal Calc for $C_{24}H_{36}O_4Ni\,2H_2O$, C 59 65, H 8 34, O 19 86 found C 58 21, H 8 76
M p > 400 °C

*A note on the elemental analyses Because nickel(II) β-diketonate complexes are extremely hygroscopic, and easily bind water and solvent molecules to the axial positions on the nickel atom, it was difficult to obtain precise analyses

Epoxidation reactions
For standard conditions, all epoxidation reactions were carried out under O_2 (1 0 atmosphere) in a Schlenk tube (10 cm x 2 cm), thermostatted at 25 0 ± 0 1 °C The Schlenck tube was charged with 5 cm^3 of dried and distilled dichloromethane, to which was added 5 0 x 10 ^{4} mole alkene, 1 5 x 10 ^{3} mole aldehyde, and then the catalyst as dry compound in the amount of 1 0 mole % respective to the alkene The tube was evacuated and filled with O_2 The reaction mixture was stirred magnetically at 1000 rpm At a predetermined interval the stirrer was stopped and 1 0 x 10^{-3} mol dm^3 *o*-dichlorobenzene (internal standard) was added to the reaction mixture, (or the reaction was allowed to run until conversion of the substrate had stopped, after the internal standard was added) The volume was brought to 10 cm^3 with dichloromethane and the sample was immediately analyzed by GLC (cp sil 25 μm, temperature program 80 °C 2 0 min, 10 °C/min, 180 °C 2 0 min) Reaction products were identified by comparison to authentic samples and by GC/MS

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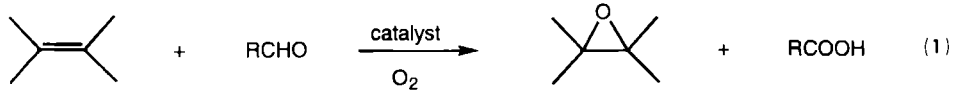
Kinetic Studies on the Epoxidation of Alkenes Catalyzed by Nickel(II) β-Diketonate Complexes in the Presence of Molecular Oxygen and an Aldehyde

6.1 Introduction

There are very few examples reported in the literature of efficient epoxidation reactions that use molecular oxygen as the oxidizing agent While molecular oxygen continues to be an attractive oxidant for industrial scale syntheses due to its ready availability, low cost, and environmentally compatible properties, it still has many problems associated with it, namely, non-selective side oxidations and, from a kinetic standpoint, comparative unreactivity [1] The difficulties associated with the use of molecular oxygen as an oxidant are discussed in detail in Chapter 2 of this thesis

Very recently Mukaiyama[2] and others[3] have published reports that molecular oxygen can be used as the terminal oxidant in the epoxidation of alkenes in the presence of a co-reductant such as an aldehyde or a primary alcohol and a transition metal catalyst such as a Ni(II), Fe(III) or Mn(III) β-diketonate complex Despite the interest generated by these reports, there has been little discussion in the literature of the mechanism of this reaction To our knowledge no thorough kinetic studies of the catalysis of alkenes to epoxides by nickel(II) β-diketonate complexes under the Mukaiyama reaction conditions (O_2/aldehyde) have been reported One report[4] has appeared in the wake of Mukaiyama's initial investigations in an attempt to explain the role of the aldehyde in the reaction and another, by Katsuki,[5] describes an investigation using chiral Ni(II) salen-type catalysts in which no enantioselectivity of the product epoxides was found In Chapter 5 we described our results on the scope and efficacy of reaction (1)

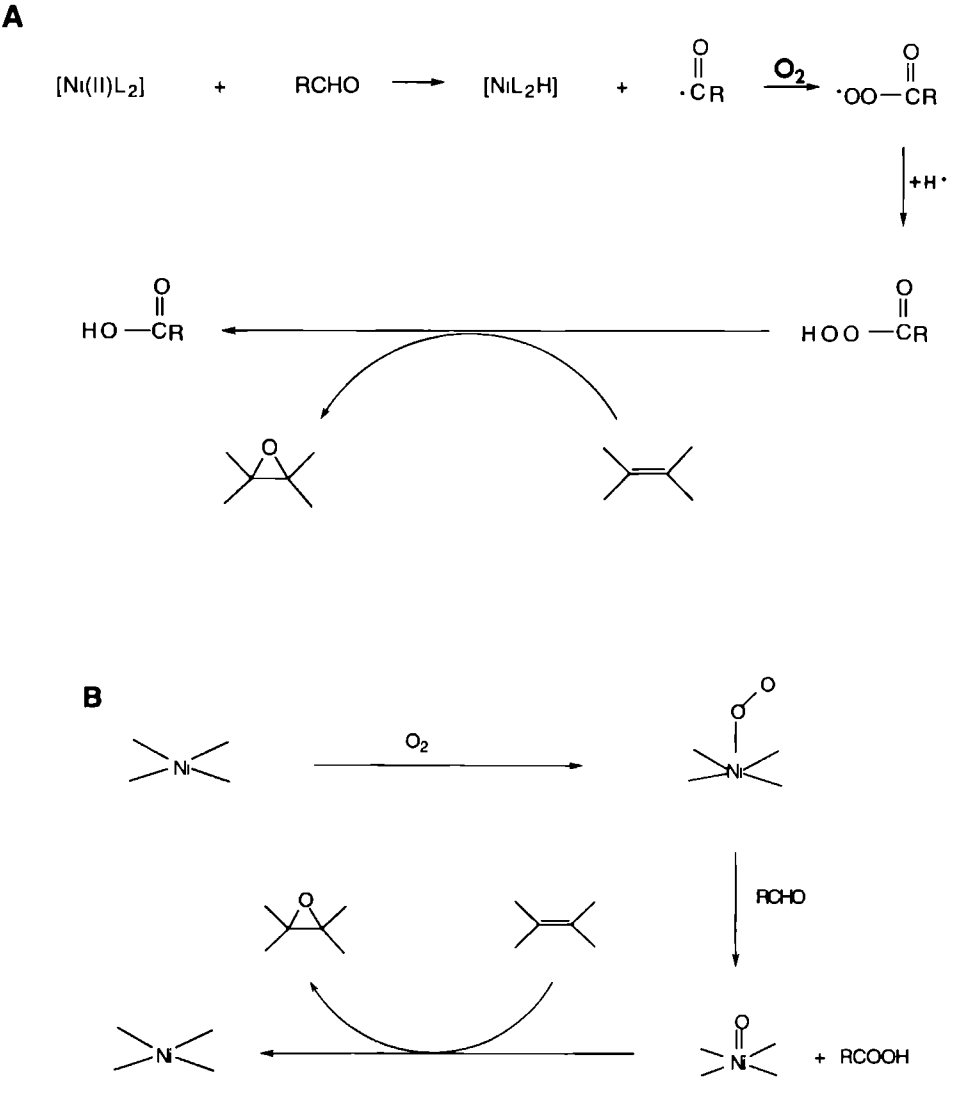


(1)

We have also carried out an extensive study of the reaction mechanism of (1) in order to understand the nature of the reaction and to identify the active oxidizing species The results of this investigation are described in this chapter

It has been known since the beginning of this century that it is possible to prepare peroxy acids by the auto-oxidation of aldehydes in the presence of UV radiation or transition metal salts [6] Several peroxy acids, including peroxy acetic acid and peroxy benzoic acid have been prepared in this way using metallo-porphyrins as catalysts [7] Unsaturated aldehydes such as methacrolein gave mostly acidic polymers as auto-oxidation products in the presence of transition metal salts such as cobalt(II) acetate and manganese(II) acetate [8] Because peroxy

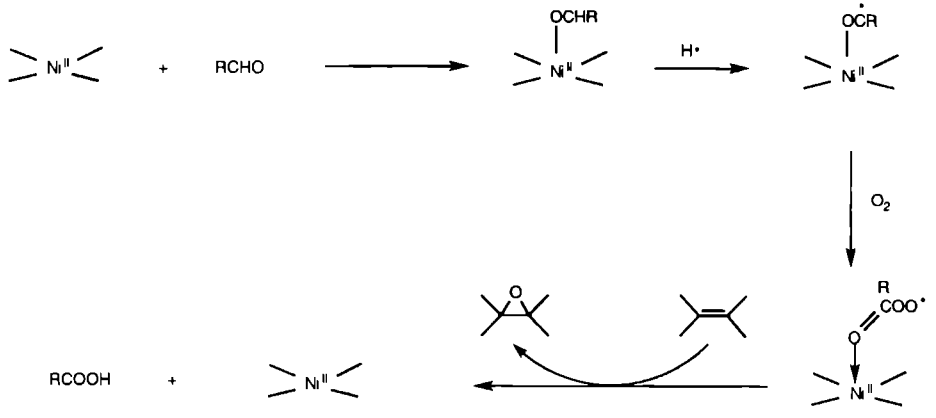
acids are powerful epoxidizing reagents in their own right,[9] it seemed natural to assume that reaction (1) proceeds through a peroxy acid intermediate--formed by the auto-oxidation of the aldehyde--which is the actual epoxidizing agent The only role of the transition metal catalyst in this scenario, therefore, is to catalyze the formation of the peracid (mechanism **A** in Scheme 6 1)



Scheme 6.1 *Two possible mechanisms for the epoxidation of alkenes in the presence of molecular oxygen and an aldehyde In an auto-oxidation, the nickel complex catalyzes the formation of a peroxy acid from the aldehyde, which is then the active epoxidizing agent (A) A nickel-oxo complex is formed by direct bonding of the O_2 molecule to the nickel catalyst (B)*

Another possible mechanism, implied by Mukaiyama in his initial reports,[2] is the formation of a nickel-dioxygen species where one oxygen atom is accepted by the reductant (aldehyde) to form the corresponding carboxylic acid and the nickel-oxo species, the purported active oxidizing agent that converts alkene to epoxide (mechanism **B** in Scheme 6 1)

An alternative mechanism for the epoxidation of alkenes by Ni(II) β-diketonate complexes in the presence of O_2 and an aldehyde, that has not been previously suggested or implied in the literature is shown in Figure 6 1



Scheme 6.2 *Possible mechanism for reaction (1) where a nickel-peroxo species is formed which is the active oxygen transfer agent*

This proposed mechanism involves coordination of the aldehyde to the nickel atom of the catalyst, abstraction of a hydrogen atom to give an acyl radical that is bound to the metal, subsequent reaction of O_2 to give a metallo-peroxy radical species which, possibly *via* a cyclic intermediate (Figure 6 1), effects the transfer of an oxygen atom to the alkene substrate to give the epoxide and the corresponding carboxylic acid

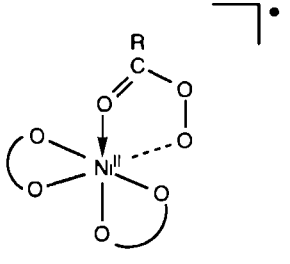
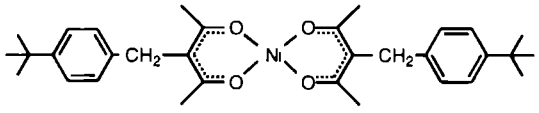


Figure 6.1 *Possible cyclic intermediate (nickel-peroxy species) that could carry out oxygen transfer to an alkene*

6.2 Results

6.2.1 Description of the catalytic system

The standard conditions used in the epoxidation of alkenes by Ni(II) β-diketonate complexes in the presence of an aldehyde are as follows: A Schlenk tube was charged with 4.8 cm^3 of dry distilled dichloromethane. The alkene (0.5 x 10^{-3} mol), aldehyde (1.5 x 10^{-3} mol), and dry catalyst (5.0 x 10^{-6} mol, 1.0 mol % respective to the alkene) were added to give a total concentration of 0.1 $mol.dm^{-3}$, 0.3 $mol.dm^{-3}$ and 0.001 $mol.dm^{-3}$ for the alkene, aldehyde, and catalyst, respectively. The reaction was magnetically stirred under 1.0 atmosphere of oxygen at a rate of 1000 rpm. The reaction vessel was thermostatted at 25.0 °C Except where noted, kinetic experiments were carried out with α-pinene as alkene substrate, isobutyraldehyde as co-reagent, and bis-(3-*t*-butylbenzyl-2,4-pentanedionato)-nickel(II) **1** as catalyst .



1

6.2.2 Kinetics

6.2.2.1 Reaction order

The catalytic reaction (1) was followed by monitoring the disappearance of the substrate and the appearance of the product epoxide as a function of time. All reactions were followed by gas chromatography.

Effect of varying the substrate, aldehyde, O_2, and catalyst concentrations

The order in substrate was determined by following the decrease in substrate (or the increase in epoxide) over time. In the presence of excess isobutyraldehyde (6 0 mol equivalents respective to the alkene concentration), the reaction was zero order in substrate up to a conversion of 80% (Figure 6.2) with a zero order rate constant of 2.13 x 10^{-5} $mol.dm^{-3}s^{-1}$ under the conditions, [catalyst] = 1 0 x 10^{-3} mol dm^{-3}, [aldehyde] = 0 6 $mol.dm^{-3}$, [alkene] = 0 1 $mol.dm^{-3}$.

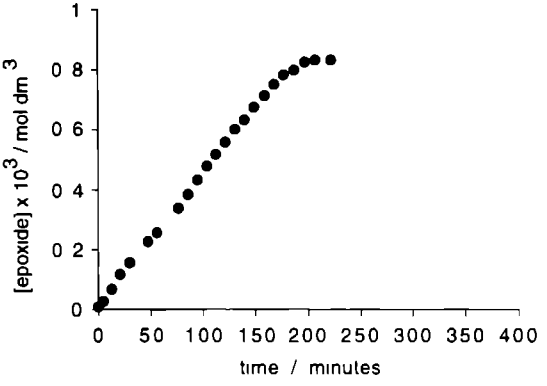


Figure 6.2 Epoxidation of α-pinene vs time in the presence of an excess (6 0 mol equivalents, respective to alkene) of isobutyraldehyde Standard conditions, except that the concentration of isobutyraldehyde = 0 6 mol dm ^{3}

In the presence of a reduced concentration of aldehyde (2 0 mole equivalents respective to the concentration of alkene), however, the reaction gave first order kinetics in the disappearance of substrate as shown in Figure 6 3

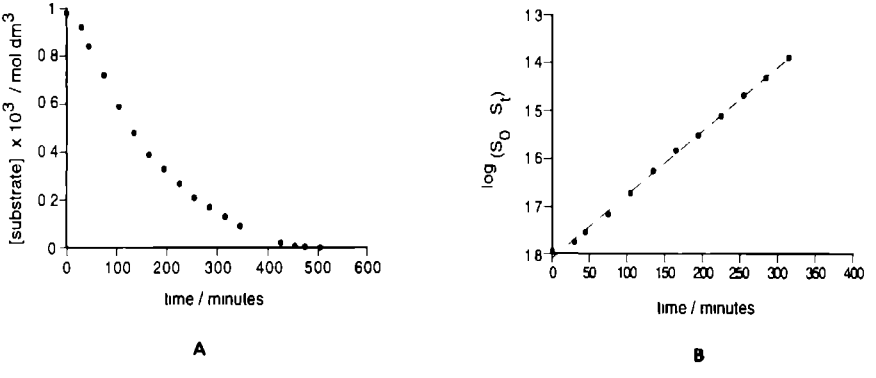


Figure 6.3 Decrease in substrate vs time in the presence of 2 0 mole equivalents of isobutyraldehyde (A) Standard conditions except that the concentration of isobutyraldehyde = 0 2 mol dm ^{3} Data from (A) fitted to a first order rate equation (B)

The rate of epoxide formation was equal to the rate of substrate conversion in both cases shown in Figures 6 2 and 6.3. The data in Figure 6.3A (up to 80% conversion) was fitted to a first order rate equation (shown in Figure 6 3B), giving a first order rate constant of 2 21 x 10^{-6} s^{-1}.

Although different substrates were epoxidized at varying rates as shown in Chapter 5, all substrate conversions showed first order kinetics in substrate if 2.0 mol equivalents of aldehyde were present in the reaction mixture. At 3.0 mol equivalents of aldehyde, which was used for the epoxidation reaction conditions described in Chapter 5, the rate was zero order in substrate with a zero order rate constant of 6.41 x 10^{-6} $mol.dm^{-3}s^{-1}$.

The order in aldehyde was determined by running the reaction at different aldehyde concentrations (0 to 0.6 $mol.dm^{-3}$) and determining the initial rate of epoxide formation for each concentration of aldehyde. The results are shown in Figure 6.4.

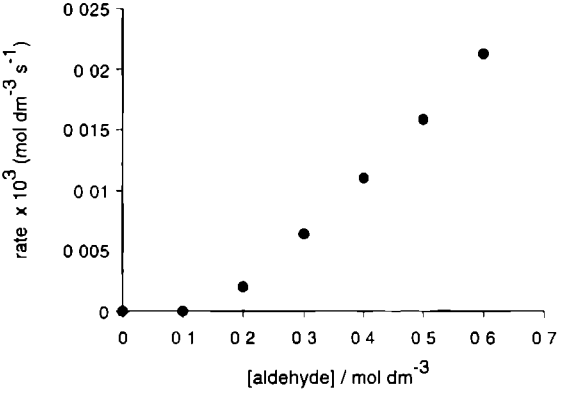


Figure 6.4 *Effect of aldehyde concentration on the initial rate. Standard conditions with varying aldehyde concentrations.*

When the concentration of aldehyde was between zero and 2.0 mol equivalents with respect to the substrate alkene, no epoxide was formed, giving a substrate conversion rate of zero. When the aldehyde concentration was equal to or greater than 2.0 mol equivalents with respect to the alkene, a linear relationship between rate and concentration was observed, indicating a first order dependence on the aldehyde (Figure 6.4) These results were observed regardless of the concentration of the reactants. Therefore, it appears that the aldehyde must be present in the reaction at a concentration of at least 2 0 mol equivalents respective to the concentration of substrate for epoxidation to occur.

The concentration of the catalyst was varied and the effect on the initial rate was determined in dichloromethane and in acetonitrile. The results are shown in Figure 6 5

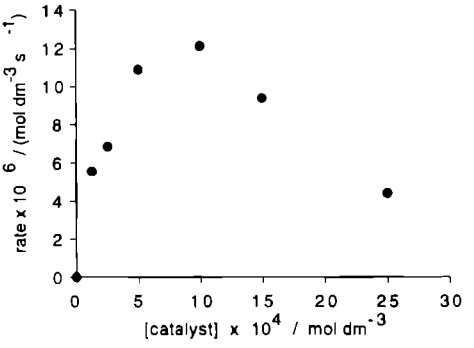


Figure 6.5 *Influence of the catalyst concentration on the rate in dichloromethane Standard conditions, varying catalyst concentrations.*

There is a more or less linear dependence of the rate on the concentration of catalyst up until a concentration of 5.0 x 10^{-4} mol.dm^{-3}. At a catalyst concentration higher than 10 0 x 10^{-4} mol.dm^{-3} (which is one mol percent respective to the alkene concentration) the rate of reaction decreased dramatically. Because this catalyst (complex **1**) can only exist in the monomeric form under the reaction conditions used,[10] aggregation of the nickel complex into a trimer is not a factor in the decrease in activity. It is possible that an increased amount of nickel catalyst acts as a radical trapping compound, which would inhibit the reaction by preventing the formation of the nickel-peroxo radical species, possibly by forming a dimeric nickel species. In our proposed mechanism, the nickel peroxo radical species precedes the formation of the active oxidizing intermediate. When the reaction was carried out in acetronitrile, four times the concentration of catalyst could be used (4.0 x 10^{-3} mol.dm^{-3}) compared to that of reactions in CH_2Cl_2, before an inhibition effect was observed (Figure 6 6). This corresponds to a catalyst concentration of 4.0 mol percent with respect to the alkene as opposed to 1.0 mole percent in dichloromethane

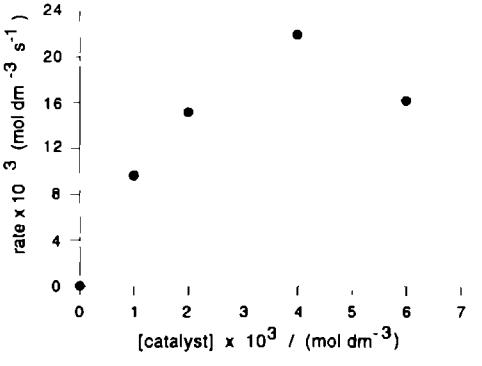


Figure 6.6 *Effect of catalyst concentration on the reaction rate in acetonitrile Standard conditions, varying catalyst concentrations.*

In order to determine the effect of the available amount of oxygen during the reaction, reaction (1) was carried out under 1.0 atmosphere of oxygen and under air (pO_2 = 160 mm Hg). The results are shown in Figure 6.7.

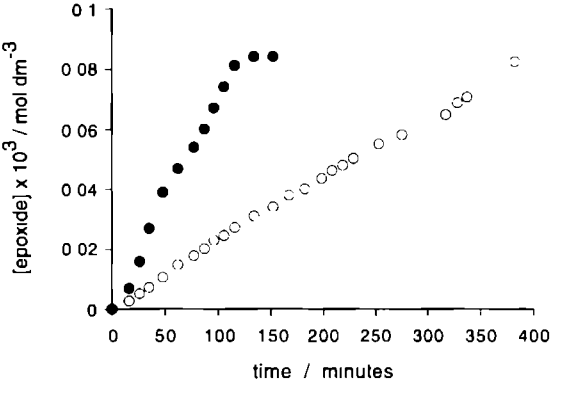


Figure 6.7 *Effect of O_2 pressure on the rate of reaction (1); 1.0 atm O_2 (•) and 160 mm Hg pO_2 (o). Standard conditions.*

At both oxygen concentrations shown in Figure 6.7, the reaction followed zero order kinetics in substrate with zero order rate constants of 1.73 x 10^{-5} mol.dm^{-3}s^{-1} and 6.32 x 10^{-6} mol.dm^{-3}.s^{-1}, for the reaction at 1 0 atmosphere oxygen and 160 mm Hg O_2, respectively. The reaction is faster by 4-fold when it is carried out in the presence of 1.0 atmosphere oxygen. The difference in oxygen pressure does not effect the selectivity of the reaction for epoxidation.

6.2.2.2 Temperature studies

The temperature dependence of the rate of reaction (1) was determined by varying the temperature of the reaction and following the appearance of the product epoxide by gas chromatography as a function of time. The Arrhenius relationship derived from the temperature variation experiments is shown in Figure 6.8. The activation energy, calculated from these data was found to be 48 ±6 kJ/mol.

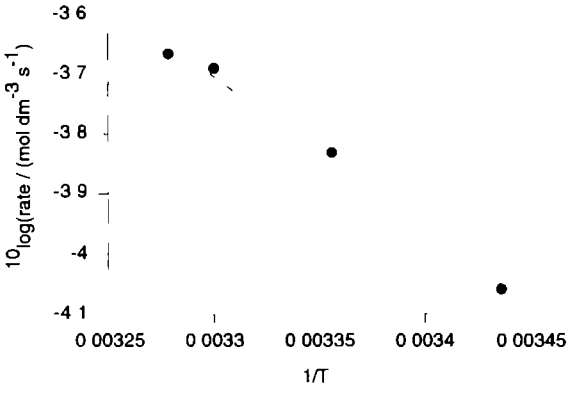


Figure 6.8 *Arrhenius plot of the temperature dependence of reaction (1) Standard conditions except, [α-pinene] = 0 1 mol dm ^{3}, [isobutryaldehyde] = 0 4 mol dm ^{3}*

The Eyring relationship shown in Figure 6.9 was used to calculate the energy parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ which are 46 ±6 kJ/mol and -116 ±6 J mol^{-1}K^{-1} respectively

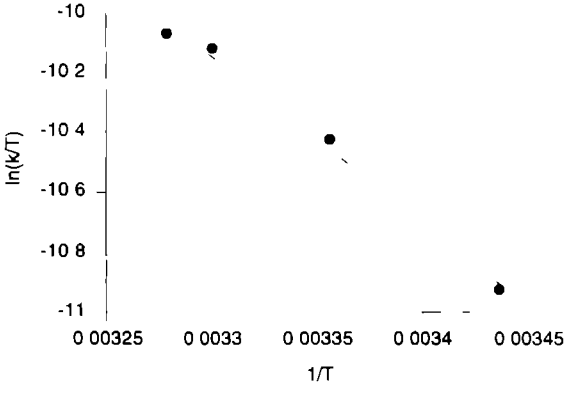


Figure 6.9 *Eyring plot of the temperature dependence of reaction (1) Standard conditions except [isobutyraldehyde] = 0 4 mol dm ^{3}*

The large negative value of $\Delta S^{\ddagger}$ points to a rigid transition state of the rate-determining reaction step

6.2.3 Titration experiments

When a pale pink solution of complex **1** in dichloromethane was treated with isobutyraldehyde (in air), it immediately turned green and the broad peak at 520 nm in the visible region of the absorption spectrum disappeared This color change, and the disappearance of the 520 nm

peak is indicative of a structural change of the catalyst from square planar to a five-coordinated pyramidal or a six coordinated octahedral complex [11,12] Because nickel(II) is a d^8 ion, this geometric change from square planar coordination, is accompanied by an electronic change from the diamagnetic to the paramagnetic state Ni(II) β-diketonate complexes are Lewis acids, and strong Lewis bases such as pyridine bind to the nickel ion in a two-to-one fashion [13]

$$NiL_2 + py \rightleftharpoons NiL_2py \qquad \text{(step 1)}$$

$$NiL_2py + py \rightleftharpoons NiL_2py_2 \qquad \text{(step 2)}$$

Although isobutyraldehyde is a much weaker ligand than pyridine, the binding of the aldehyde to the nickel ion of the catalyst can be successsfully measured by following the disappearance of the peak at 520 nm as a function of aldehyde concentration The results are shown in Figure 6 10

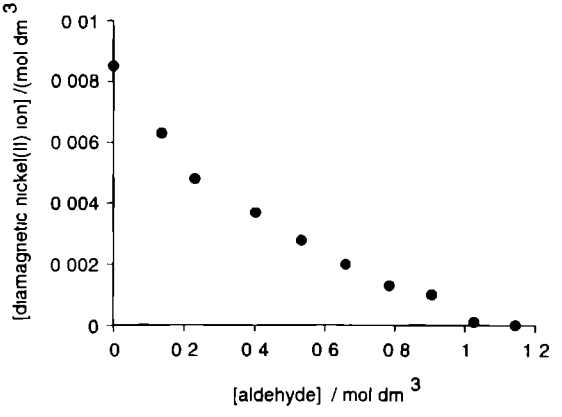


Figure 6.10 *Titration of complex 1 with isobutyraldehyde in dichloromethane*

Isobutyraldehyde is a relatively weak ligand that must be present in large excess to bind at least one coordination site on all the nickel atoms present in solution (Figure 6 10) The binding of an aldehyde molecule to the nickel(II) atom converts the complex from diamagnetic to paramagnetic The data in Figure 6 10 can be fitted to an equation that is defined for a 1 1 complex, with a binding constant of $K_a = 0\ 68 \pm 0\ 08$ dm^3 mol^{-1} Whether or not the vacant sixth coordination site on the nickel atom is bound by aldehyde at higher concentrations is not possible to determine from these measurements Certainly at least one aldehyde is bound to the catalyst under the reactions conditions used for epoxidation where a 300-fold excess of isobutyraldehyde (with respect to the catalyst) is present

6.2.4 Mechanistic probes: determination of the presence of radical species

When a radical trapping compound such as 2-*t*-butyl-4-methylphenol[14] was added to the reaction mixture during the reaction, epoxidation stopped immediately (Figure 6 11, arrow) When 2-*t*-butyl-4-methylphenol was added at the beginning of the reaction, no epoxide was formed

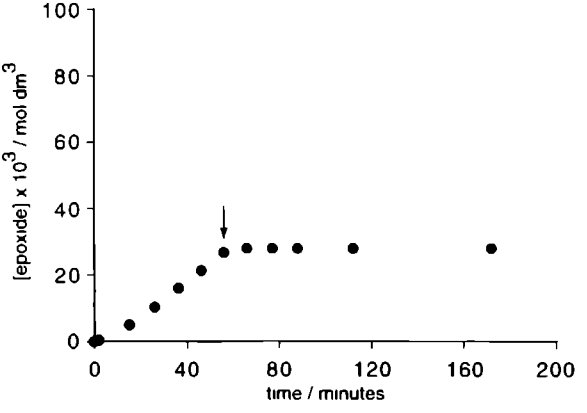


Figure 6.11 *A radical trapping compound (2-t-butyl-4 methylphenol), added to the reaction mixture after 55 minutes (arrow), quenches the reaction Standard conditions*

These results indicate that the formation of a radical species in the reaction mixture is crucial for epoxidation to occur Furthermore, in the presence of a radical inhibitor, no conversion of the substrate to other oxidation products was observed

Cyclobutanol is frequently used as a mechanistic probe to determine the nature of the oxidizing species in a particular reaction [15] Splitting of the carbon-carbon bond of cyclobutanol to give 4-hydroxybutyraldehyde is indicative of an oxidizing species of a radical nature, while the oxidation of cyclobutanol to cyclobutanone is compatible with a two electron oxidant When cyclobutanol was used as the substrate in a reaction with complex **1** as catalyst and isobutyraldehyde as reductant, only 4-hydroxyaldehyde was produced

A series of aldehydes was tested under the standard reaction conditions with complex **1** as catalyst in order to determine their effect on the efficiency of the epoxidation reaction and to determine whether a radical species plays a role in the reaction mechanism It is known that acyl radicals can form from aldehydes in the presence of transition metals[16 7 8] For stability reasons, such a species might be bound to the metal center (See Scheme 6 2)

We investigated whether the reactivity of a variety of aldehydes as co-reductants in reaction (1) correlates with the stability of their corresponding acyl radicals [8] For example, the aromatic ring of benzaldehyde can stabililize the unpaired electron of the corresponding acyl radical by distributing the electron density in the π-system Conjugated aldehydes such as cinnamaldehyde and crotonaldehyde can have a similar stabilizing ability Alkyl aldehydes including

isobutyraldehyde and butyraldehyde will generate unstable and therefore reactive acyl radicals which can effect the epoxidation of alkenes α-Pinene was used as a test alkene in these reactions and the results are shown in Table 6 1 Aryl or conjugated aldehydes such as benzaldehyde and cinnamaldehyde are completely inactive as co-reductants under the reaction conditions, whereas straight-chained and branched aldehydes are active

Table 6.1 Reactivity of various aldehydes[a]

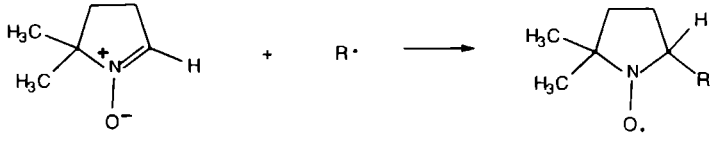
Aldehyde	% Yield α-pinene
Isobutyraldehyde	81
Butyraldehyde	5
Acetaldehyde[b]	2
Propionaldehyde	2
Benzaldehyde	0
Cinnamaldehyde	0
Pivaldehyde	68
Crotonaldehyde	0

[a]Reaction conditions 0 5 mmole α pinene 1 5 mmole aldehyde 1 0 mol % catalyst 5 0 cm^3 dichloromethane 1 0 atmosphere O_2, 25 °C
[b]Due to its low boiling point the reaction with acetaldehyde was carried out at 15 °C

The branched aldehydes, isobutyraldehyde and pivaldehyde, are excellent co-reductants, which gave yields of α-pinene epoxide of 81% and 68%, respectively These results suggest that an acyl radical can indeed be an intermediate species in the epoxidation reaction described here Investigations into a heterogenous epoxidation system by Laszlo and co-workers, using kaolinite and an aldehyde in the presence of O_2, yielded similar aldehyde reactivities [17]

EPR studies using a spin-trap

It is possible to determine the presence of radicals in a reaction, and to some extent identify them, by the use of spin traps' and the identification of their radical adducts by Electron Paramagnetic Resonance (EPR) spectroscopy We investigated the epoxidation of alkenes by nickel complex **1** in reaction (1) with the radical trap 5,5-dimethyl-1-pyrroline-1-oxide, DMPO (**2**), using these techniques to determine whether or not radical species play a role in the reaction



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In one set of experiments, samples containing the various components of reaction (1) (nickel catalyst **1**, isobutyraldehyde, O_2, and α-pinene or *cis*-stilbene) were frozen directly after addition of DMPO, and their EPR spectra were measured at 15 K. No signal other than that of the cavity was observed. After the samples were thawed and allowed to stand at room temperature for 5 minutes and refrozen, EPR signals were observed in several samples (Table 6 2) The fact that signals were observed only in the presence of DMPO is evidence of the spin adduct nature of the EPR-active species. Samples containing **1**, isobutyraldehyde, and the spin trap showed a signal at g = 2.00 and a shoulder at g = 2.02. The relative intensity of these signals varied when attempts were made to exclude oxygen from the sample. This observation is consistent with the trapping of two different radicals, e.g. the C-centered alkoxy radical, and the peroxy radical (the latter forming only in the presence of O_2, as proposed in the mechanism in Scheme 6.2) Interestingly, radicals were formed also from α-pinene and *cis*-stilbene in the presence of **1**, but in the absence of isobutyraldehyde.

Table 6.2 EPR signals from spin-trap experiments in CH_2Cl_2

Sample	Frozen, t = 0	t = 5 min	Room temperature
(A) **1**, ald, DMPO	none	signal at g = 2 00	major, but unstable signal (a_N 12 7 G, $a_{H\beta}$ 9.8 G)
		shoulder at g = 2 02	minor stable signal (a_N 13.2 G)
(B) DMPO	-[a]	-	none
(C) **1**, ald, O_2 (no DMPO)	none	none	none
(D) **1**, α-pin, O_2, DMPO	none	single line at g = 2.00	stable signal (a_N 13 1 G, $a_{H\beta}$ 8.4 G, $a_{H\gamma}$ 1 5 G)
(E) **1**, α-pin, O_2	-	-	none
(F) **1**, α-pin, ald, O_2, DMPO	-	-	(signal as in (D) and unstable signal as in (A) ultimately a_N 13 3, $a_{H\beta}$ 8.7 G
(G) **1**, α-pin, ald, O_2 (no DMPO)	-	-	none
(H) **1**, stilb, DMPO	none	single line at g = 2 00	-
(I) **1**, O_2 (no DMPO)	none	none	

[a]Not measured
1 = Bis-3-(p-t-butybenzyl-2,4-pentanediono)-Ni(II), ald = isobutyraldehyde, α-pin = α-pinene, stilb = *cis*-stilbene

The N and H hyperfine splittings, characterized by a_N and a_H, respectively, which can be used for identification of the DMPO spin adducts,[18] were not observed in the powder spectra obtained from the frozen solutions. In a separate experiment, new spectra were measured at room temperature and the development of the signals was followed over time As in the first set of experiments, detectable amounts of radicals were observed only in the presence of DMPO, indicating both the radical nature and the transient character of the intermediates. The spectrum of sample (A), containing **1**, isobutyraldehyde, and DMPO showed two spin adducts, which is in agreement with the result from the frozen sample. One of the spin adducts

with values for a_N and $a_{H\beta}$ of approximately 12 7 and 9 8 G, respectively, had the higher intensity to start with, but decayed a factor 2 5 lower in intensity in 90 min The other spin adduct with a_N approximately 13 2 G ($a_{H\beta}$ not identified, multiplet with a H_γ) of approximately 1 5 G reached its maximum intensity after 90 min Sample (D), with **1** , α–pinene, O_2 and DMPO showed a stable signal (no decrease in intensity after 165 min), different from that obtained with aldehyde included, with values for a_N, $a_{H\beta}$, and $a_{H\gamma}$ of approximately 13 1, 8 4 and 1 5 G Sample (F), containing **1**, α-pinene, isobutyraldehyde, O_2, and DMPO, initially showed the unstable signal observed in sample (A) However, after 150 minutes this signal had decayed completely and was replaced by the signal observed in sample (D), which was initially observed only at a very low intensity

Comparison of the a_N an a_H values with those reported in the literature with benzene as the solvent[18] allows a tentative identification of some of the spin adducts and therefore of the radicals trapped Keeping the difference in solvent in mind, the resemblance of the set of hyperfine splittings of the unstable signals in (A) to those reported for a benzoyloxy radical adduct in benzene (a_N and $a_{H\beta}$ of approximately 12 24 and 9 63 G, respectively) points to the trapping of a radical that gave an unambiguous $a_{H\gamma}$ splitting pattern in the spectrum of the more stable signal in (A) Although it is not possible to identify it, the a_N value of approximately 13 2 G would indicate that it has been trapped as an O- rather that a C-centered radical if it is due to a radical directly derived from the aldehyde The relatively low value for a_N and especially for that of $a_{N\beta}$ for the EPR signal in (D) would point to the trapping of an alkoxy rather than an alkyl radical The values for the hyperfine splittings of the EPR signals of radical adducts from (A) and (D) are sufficiently different to discount the possiblity that the same radical, derived, for example, from the acetylacetonate ligand, is trapped in both cases It is likely that the radical in (D) is derived from α-pinene, and not from acetylacetonate, as no signals were observed in the absence of the alkene

In the hematin/cumene hydroperoxide system reported in the literature, no radicals were trapped, and the EPR signals observed were due only to oxidation of the spin trap[19], resulting in 5,5-dimethyl-pyrrolidone-(2) oxyl-(1), DMPOX)[20] The possibility that this compound was formed in our system could be ruled out, as the a_N and a_H values reported for this radical in solvents related in polarity to dichloromethane are different from those observed by us (benzene, a_N 6 45 and a_H 3 28, chloroform, a_N 6 58, and a_H 3 60[20])

6.2.5 Stereochemistry of the products

We found that in reactions with *cis*-alkenes such as *cis*-stilbene the stereochemistry of the product epoxide is not conserved, indicating that the oxygen insertion step is non-concerted (Table 6 3)

Table 6.3 Stereoselectivity of the epoxidation of *cis*-stilbene catalyzed by different nickel complexes[a]

Entry	Catalyst	% Conversion	% Epoxide	*cis/trans* ratio
1	Complex **1**	40	36	1 13
2	Complex **1** and pyridine	47	46	1 45
3	Complex **1** and m CPBA	63	65	3 1
4	m CPBA	60	60	100% cis
5	Ni(II)salophen	70	53	1 10
6	Ni(II)TPP	80	68	1 12
7	$Ni(II)OAc_2$	71	69	1 22

[a]Reaction conditions 0 5 mmol *cis* stilbene, 1 5 mmol isobutyraldehyde 1 0 mol % catalyst 5 0 cm^3 dichloromethane 1 0 atmosphere O_2 25 °C

Complex **1** (entry 1) gave a yield of 36% *cis*-stilbene epoxide with a substrate conversion of 40% before the catalyst became degraded and was no longer active The *cis/trans* ratio of the product was 1 13 This result indicates that the product is formed by a step-wise oxygen insertion process, whereby rotation around the single bond occurs (See A, Figure 6 12) and not by a concerted mechanism (B, Figure 6 12) In the presence of a small quantity of pyridine, (entry 2) the *cis/trans* ratio was shifted to 1 45, which could indicate that a small fraction of the products are formed *via* a concerted pathway, which is inhibited by the presence of a coordinating ligand such as pyridine Using Ni(II) salophen or Ni(II) tetraphenylporphyrin as catalyst (entries 5 and 6), gave similar *cis/trans* stilbene epoxide ratios as did complex **1** Interestingly, Ni(II) salophen and Ni(II)TPP gave higher overall yields of epoxide when compared to complex **1**, although the selectivity in both cases was slightly lower, 75% and 85% selectivity for Ni(II) salophen and Ni(II)TPP, respectively, while complex **1** gave a selectivity for epoxide of 90% The nickel salt, Ni(II) acetate tetrahydrate afforded a good yield of epoxide (69%) with very high selectivity (97%) and a *cis/trans* product ratio of 1 22, producing twice as much *trans* stilbene epoxide for every *cis*-stilbene epoxide molecule formed when compared to the reaction catalyzed by complex **1** (entry 1) Epoxidation of *cis*-stilbene by *m*-CPBA (entry 4) gave exclusively *cis*-stilbene epoxide as was expected for an epoxidizing agent that confers oxygen transfer to the alkene *via* a concerted mechanism so that the stereochemistry of the products is conserved When a catalytic amount of complex **1** was added to the reaction mixture that included *m*-chloroperoxy benzoic acid (entry 3), the product ratio changed from 100% *cis*-stilbene epoxide to a ratio of 3 1, *cis/trans* From these results it appears that the nickel catalyst is involved in the oxygen transfer step

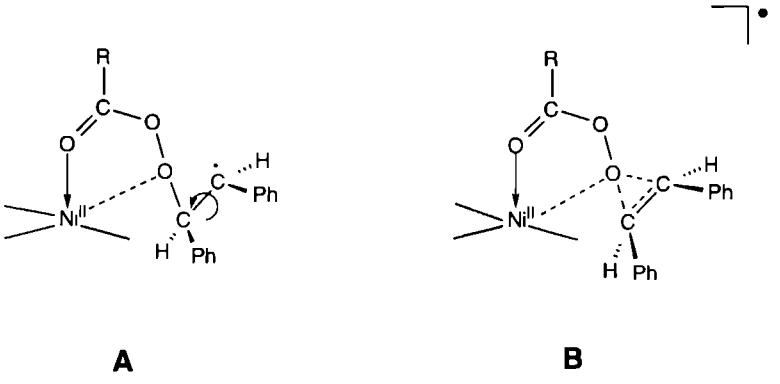


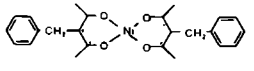
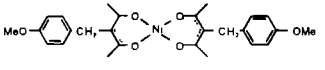
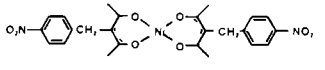
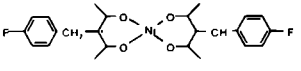
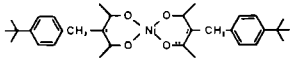
Figure 6.12 Step-wise oxygen addition (A), and concerted oxygen addition step to the double bond of the alkene (B).

6.2.6 Electronic effects of para-substituents on the benzene ring

The activity and efficiency of many transition metal catalysts can be altered by modifying the ligand around the metal with electron donating or withdrawing substituents. Changing the electron density around the metal ion can either stabilize or destabilize the catalyst in terms of its affinity for binding oxidant molecules or during the oxygen transfer step. In the case of metallo-porphyrins and Mn(III) salen complexes, it was found that the presence of electron withdrawing groups on the ligand ring enhanced the rate of epoxidation.[21]

We varied the substituents at the para-position of the benzene ring in an attempt to discern the effect a change in electron density on the nickel atom would have on the turnovers per hour achieved by the catalyst The results are shown in Table 6.4.

Table 6.4 Effect of para-substituents on the turnover rate of nickel(II) β-diketonate catalysts[a]

Catalyst	Turnover # / h
	11
	32
	39
	24
	21

[a]Reaction conditions 0 5 mmol α-pinene, 1.5 mmol isobutryaldehyde, 1 0 mol % catalyst, 5 0 cm^3 dichloromethane, 1 0 atmosphere O_2, 25 °C Estimated error in the turnover numbers is ~5%

There is a small, but significant, effect on the turnover rate of α-pinene by the catalyst when the para-position of the benzene ring of the nickel complex is modified with either electron-withdrawing or sending groups It is unlikely then, that the oxidation of alkene substrates to epoxides occurs outside the nickel sphere as has been suggested by Katsuki.[6] Substitution of the benzene ring with a nitro group gave a catalyst that achieved the highest turnover numbers (39) as compared to only 11 turnovers per hour of the unmodified catalyst. A strongly electron-withdrawing group such as a fluorine atom appeared to slightly decrease the turnover number compared to that of the nitro-group modified catalyst. The difference in turnover numbers depicted in Table 6.4 could also be explained by a greater stability imparted to the catalyst by modification of the benzene ring. Attempts to establish a Hammet correlation with substituted styrenes were unsuccessful due the poor reactivity of styrene and its derivatives under the applied reaction conditions.

6.2.7 Solvent effects

The effect of solvent on the rate of epoxidation of α-pinene is shown in Figure 6.13. Epoxidation of α-pinene in DMF and EtOH does not occur, most likely due to strong coordination of solvent molecules at the vacant fifth and sixth positions on the nickel(II) atom One of these positions must be occupied by an aldehyde molecule for the reaction to proceed

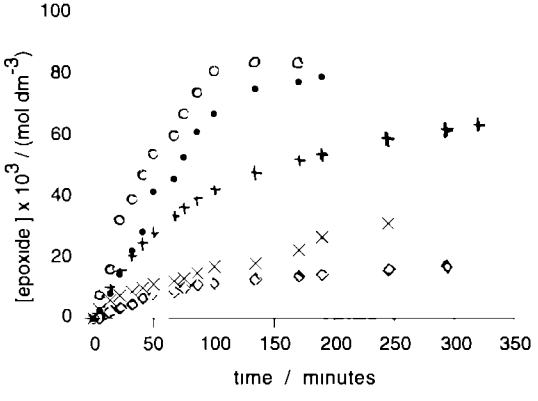


Figure 6.13 *Solvent effects on reaction (1) Dichloromethane (o), acetonitrile (•), toluene (+), tetrahydrofuran (x), and acetone (◇).Standard conditions.*

Weakly coordinating solvents such as tetrahydrofuran and acetone retard the reaction, but do not inhibit the conversion of substrate to epoxide. Acetonitrile is a coordinating solvent, giving only a slightly lower rate than that observed in the non-coordinating solvent, dichloromethane (zero order rate constants are 1.27 x 10^{-5} mol.dm^{-3}.s^{-1} and 1.73 x 10^{-5} mol dm^{-3}.s^{-1},

respectively). The reason for the deviating behavior of the catalyst in acetonitrile is not yet clear.

6.2.8 Effect of additives on the reaction

Reaction (1) can be inhibited by "poisoning" the catalyst with competing coordinating Lewis bases such as pyridine. These results are shown in Figure 6.14. Pyridine is a much stronger Lewis base than is isobutyraldehyde and is able to successfully compete for the vacant fifth and sixth coordination sites on the square planar nickel(II) catalyst.

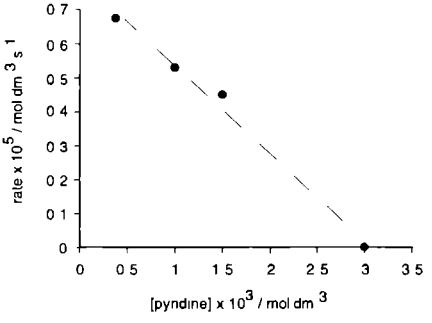


Figure 6.14 *Effect of pyridine on the reaction rate. Standard conditions.*

At equal mole equivalents of pyridine and aldehyde (1.5 x 10^{-3} mol.dm^{-3}), the rate of the reaction was reduced by 45%. At twice the molar equivalent of aldehyde, the presence of pyridine in the reaction was able to completely inhibit the conversion of substrate. Furthermore, the addition of pyridine to the reaction mixture changed the order of the reaction in substrate from one to zero when a 2:1 aldehyde/substrate molar ratio was used. This change in order can be explained by a change in the rate limiting step.

To determine if product inhibition was a factor in the course of the reaction, the effect of adding isobutyric acid to the reaction mixture was investigated. The results are shown in Figure 6.15.

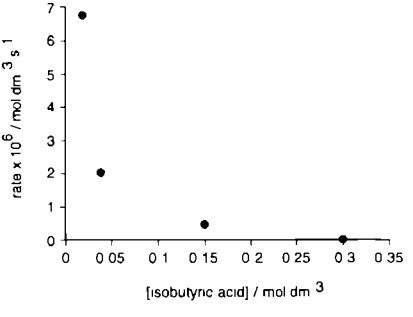


Figure 6.15 *Effect of isobutyric acid on the rate of reaction (1). Standard conditions*

The addition of isobutyric acid to the reaction mixture does inhibit the rate, but only when it is present in high concentrations. Reaction (1) is normally carried out with 1.5 x 10^{-3} mol dm^{-3} isobutyraldehyde meaning that, if the reaction goes to completion, only 1.5 x 10^{-3} mol.dm^{-3} of isobutryic acid is present in the solution at the end of the reaction. At this concentration, isobutyric acid does not affect the rate. Only at higher concentrations (0.05 mol.dm^{-3}) was an effect observed, and at very high concentrations, (0.15 - 0.3 mol.dm^{-3}) the reaction was effectively retarded. This result is in agreement with the order of ligand binding strength. Isobutyric acid is a much weaker ligand than is isobutyraldehyde, meaning that a much higher concentration of the acid is needed to compete with isobutyraldehyde for the coordination sites on the nickel atom. The addition of isobutyric acid to the reaction mixture was found to cause a change in the reaction order in substrate from one to zero when a 2:1 aldehyde/substrate molar ratio was used. As with the results obtained from the addition of pyridine to the reaction, the change in reaction order in substrate from one to zero can be explained by a change in the rate limiting step. This will be discussed in more detail in Section 6.3.

6.3 Discussion

Based on the results presented in the previous sections, reaction (1) can be described by Scheme 6.3

$$Ni^{II}L_2 \overset{RCHO}{\rightleftharpoons} Ni^{II}L_2\,RCHO \qquad (1.1)$$

$$Ni^{II}L_2RCHO \overset{-H\cdot}{\rightleftharpoons} [Ni^{II}L_2RCO]\cdot \qquad (1.2)$$

$$[Ni^{II}L_2RCO]\cdot \overset{O_2}{\rightleftharpoons} [Ni^{II}L_2RCOOO]\cdot \qquad (1.3)$$

$$[Ni^{II}L_2RCOOO]\cdot \rightleftharpoons \overline{[Ni^{II}L_2RCOOO]}\cdot \qquad (1.4)$$

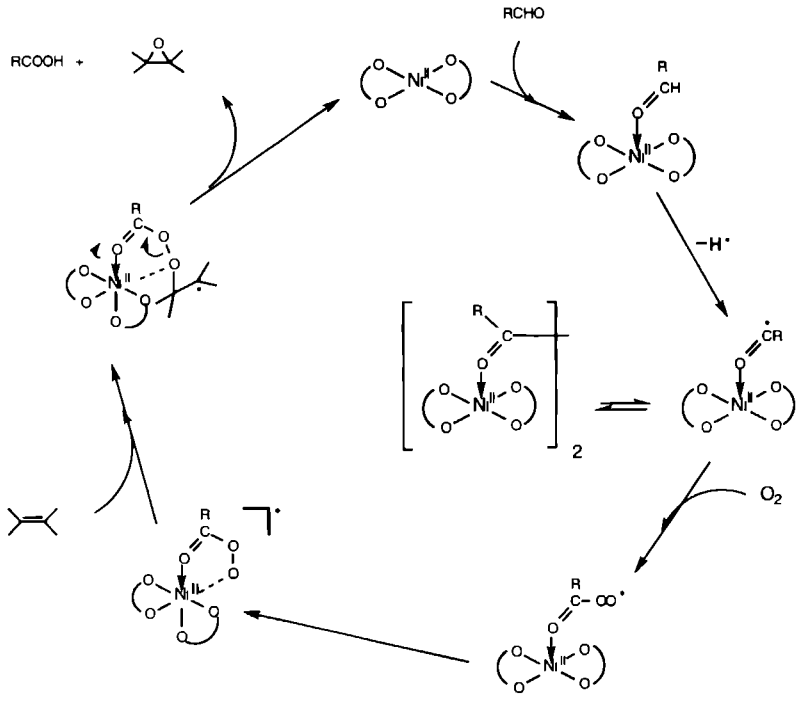
$$\overline{[Ni^{II}L_2RCOOO]}\cdot \overset{alkene}{\rightleftharpoons} Ni^{II}L_2 + RCOOH + \text{epoxide} \qquad (1.5)$$

Scheme 6.3 *Proposed reaction sequence of reaction (1). L = β-diketonate ligand.*

In the reaction sequence proposed in Scheme 6.3, the aldehyde binds to one of the vacant coordination sites on the Ni(II) atom as the first step (1.1), and then an acyl radical (that is still bound to the metal) is formed in a subsequent step (1,2). In the following step, a molecule of dioxygen is taken up to give a Ni(II) peroxo radical species (1.3) The nickel atom is formally reduced to nickel(I) as a result of the formation of a cyclic metallo-peroxo species is (1.4) This

nickel-peroxo species is the proposed oxidizing species responsible for the oxygen atom transfer to the alkene (1 5)

The two mechanisms suggested earlier in this chapter (Scheme 6 1A, B) have been rejected by us as unlikely for several compelling reasons Mechanism (B) of Scheme 6 1 suggests that a nickel-oxo complex is formed as a result of the direct reaction of the nickel(II) center of the catalyst with molecular oxygen, and that the dioxygen bond is split so that an aldehyde molecule accepts one of the oxygen atoms to give the corresponding carboxylic acid Although this scenario is consistent with the stoichiometry of the reaction, there is no evidence that Ni(II), when coordinated by oxygen ligands, is capable of directly binding molecular oxygen, based on the extensive studies carried out in this area that are described in the literature [22] In our own investigations we also found no spectroscopic evidence of molecular oxygen binding directly to the nickel atom of the catalyst Mechanism (A) in Scheme 6 1 seems plausible due to the wealth of evidence described in the literature[7 8 9 16] concerning the auto-oxidation of aldehydes to form peroxy acids Because peroxy acids have been traditionally used as powerful and highly selective epoxidation agents it seems logical that a peroxy acid, formed *in situ* as the result of the autooxidation of the aldehyde, is the epoxidizing species However, this assumption is at variance with the reactivity of aldehydes observed during our investigations as well as those of Mukaiyama Benzaldehyde, which has been reported to be easily converted to its corresponding peroxy acid in the presence of a number of transition metals,[6 7 9] is unreactive under the reaction conditions described here and in Chapter 5 of this thesis Stronger evidence, discounting an *in situ* formed peroxy acid as the active epoxidizing agent, is found by examining the stereochemistry of the products when a *cis* alkene such as *cis*-stilbene is used as a substrate Peroxy acids normally carry out the epoxidation of alkenes by a concerted oxygen transfer step,[9 23] so that stereochemistry of substrate is conserved in the product We found that the opposite occurs the majority product that is formed with *cis*-stilbene as substrate is *trans*-stilbene in a ratio of 1 12, or as high as 1 45 in the case where pyridine was added to the reaction The small amount of *cis* epoxide that was formed in these reactions is likely the result of a metal-peroxo transfer step where closure of the epoxide ring is faster than isomerization around the single bond to form the trans-epoxide, rather than from a side reaction occurring with a peroxy acid In Scheme 6 4 is shown the proposed reaction cycle with the concurrent (proposed) structures of the catalyst and intermediates formed during the epoxidation reaction



Scheme 6.4 *Proposed mechanism of reaction (1)*

The combined results of the kinetic and other mechanistic studies have led us to conclude that the reaction is radical in nature with the formation of the bound acyl radical to be the first crucial step in the reaction and the formation of a cyclic nickel-peroxo intermediate to be the second important step The most impelling evidence for the radical nature of the reaction intermediates was found in the investigations using EPR spectroscopy These investigations pointed to the presence of two radical species One is formed in the presence of the catalyst and isobutyraldehyde in the absence of oxygen, which we propose is the acyl radical bound to the nickel center of the catalyst We propose that the second radical that is formed in the presence of oxygen is the nickel-peroxo radical species Another weaker radical signal detected with EPR techniques, was that of an alkyl radical formed in the presence of the catalyst and the alkene, but in the absence of the aldehyde The formation of this radical species may explain the trace amount of side products formed during the epoxidation reaction These side products are isomers of the alkene that are the result of rearrangement of the carbon skeleton

The epoxidation reaction can be inhibited by the addition of competing Lewis bases to the reaction mixture Reactions carried out in the presence of pyridine, a strong Lewis base relative to isobutyraldehyde, and isobutyric acid, a weak Lewis base, both slow down the rate of reaction Furthermore, the addition of pyridine or isobutyric acid changed the dependence in substrate from first order to zero order, indicating a change in the rate limiting step from step (1 5) to one of the steps before it, e g (1 3) or (1 1) (Scheme 6 5) Changing the oxygen

pressure in the reaction reduced the rate of epoxide formation, but did not change the reaction order in substrate, or the selectivity for epoxide

The reaction is first order in substrate when the ratio of aldehyde to substrate is equal to or less than 2 1 When the ratio of aldehyde to substrate is greater than 2 1, the order in substrate changes from one to zero This result can be explained by a change in the rate-limiting step from that of the interaction of the alkene with the cyclic nickel-peroxo active species (step 1 5 in Scheme 6 3) to a step preceding this one, such as the step in which the oxygen is bound (step 1 3) or the step in which the cyclic nickel peroxo complex is formed (step 1 4) An excess of aldehyde in this case could inhibit the formation of the latter intermediate by binding to a vacant position on the nickel atom, or could react with the metal-peroxo radical species Although the overall reaction rate is proportionally faster with increasing concentration of aldehyde, the above-mentioned steps would, in the case of higher aldehyde concentration, be the rate determining steps The addition of a competing coordinating Lewis base such a pyridine to the reaction also changes the order in substrate from one to zero This result can also be explained if the rate limiting step changes (see above) In the same way, high concentrations of isobutyric acid both decrease the overall reaction rate and shifts the reaction order in substrate from one to zero Catalyst concentrations greater than 1 0 x 10^{3} mol dm ^{3} in dichloromethane and 4 0 x 10^{3} mol dm ^{3} in acetonitrile, caused a slowing down of the reaction rate, probably because the proposed nickel-acyl radical or -peroxo radical is able to dimerize under higher concentrations acting as a radical trap, and thereby quenching the reaction (see Scheme 6 4)

Different alkenes are epoxidized at varying rates (see Chapter 5), but the order in substrate is independent of the structure or electronic nature of the alkene molecule In contrast to other transition metal catalysts that are used in conjunction with oxygen atom donors such as iodosylbenzene and sodium hypochlorite, where electron rich alkenes are more readily epoxidized, in the system reported here and in Chapter 5, tri-substituted electron-poor alkenes such as α pinene and limonene are epoxidized in high yields These results can be explained by the nature of electrophilic attack of the alkene on the the cyclic nickel-peroxo species that we propose as the oxygen transfer complex This complex would have a greater affinity for electron-poor alkenes Modifying complex **1** with strongly electron withdrawing groups such as fluorine, decreased the turnover numbers achieved when using an electron-poor substrate such as α pinene The observation that different alkenes react with different rates, is another indication that the rate limiting step under the applied conditions is that which involves oxygen transfer to the substrate (step 1 5)

6.4 Experimental

Materials. α-Pinene and *cis* stilbene were purchased from Aldrich and purified by chromatography over basic alumina (eluent CH_2Cl_2) Dichloromethane was dried over $CaCl_2$ and distilled before use Toluene was dried over sodium metal and distilled before use Acetonitrile was HPLC grade All other solvents were dried and distilled before use

Instrumentation. GC-analyses were carried out on a Varian 3700 gas chromatograph with a flame ionization detector, coupled to a Hewlett Packard 3395 integrator (Column CP-sil, fused silica column, 25 m, internal diameter = 25 μm) UV-visible spectra were taken on a

Perkin Elmer Lambda 5 spectrometer EPR Spectra for the low temperature measurements were taken on a Bruker Electron Spin Resonance ER-220D-LR spectrometer, and for the room temperature measurements on a Bruker ESP-300 spectrometer

Synthesis. The nickel catalyst **1** and the modified catalysts depicted in Table 6 4 were prepared and purified as described in Chapter 5, Section 5 4 of this thesis

Epoxidation reactions. All reactions were carried out as described in Section 6 2 1 No error analysis on the data was performed, but based on duplicate experiments, the error reflected in the rate constants for all rate constants measured was estimated to be 3-6%

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Nickel(II) Oxamide and Indole Complexes as Catalysts for the Epoxidation of Alkenes by Molecular Oxygen

7.1 Introduction

We have already shown that nickel(II) β-diketonate complexes are excellent catalysts for the epoxidation of unfunctionalized alkenes in the presence of molecular oxygen and an aldehyde These results are described in detail in Chapter 5 During our investigations in determining the scope of the epoxidation reaction using soluble nickel catalysts we discovered that nickel(II) porphyrins and nickel(II) salophen complexes were also good catalysts under these reaction conditions Because porphyrin and salen type compounds have already been intensively studied as macrocyclic ligands for transition metal catalysts,[1-4] we were interested in investigating the potential of oxamide and indole nickel complexes (Chart 7 1) as a new class of epoxidation catalysts using molecular oxygen as oxidant, as well as other oxygen atom donors such as sodium hypochlorite or iodosylbenzene

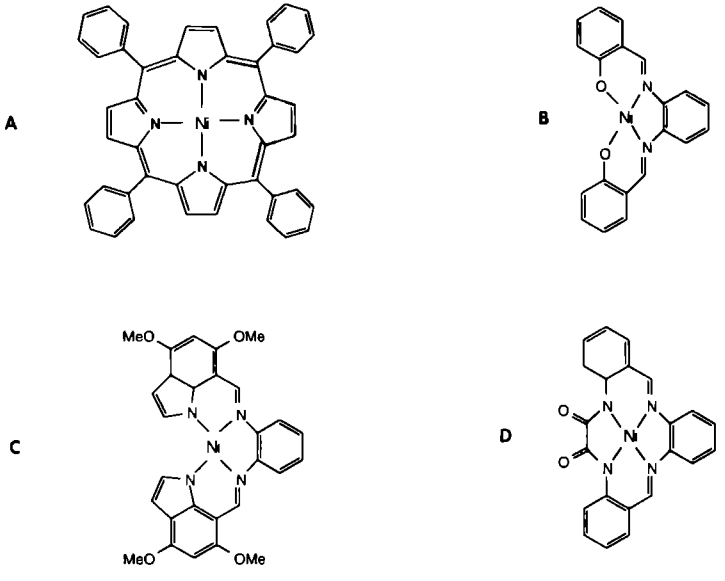


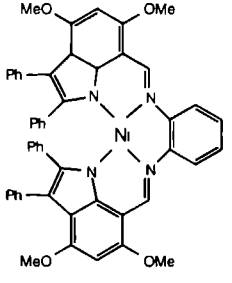
Chart 7.1 *Ni(II) porphyrin (A), Ni(II) salophen (B), Ni(II) indole (C), and Ni(II) oxamide (D) complexes*

Nickel(II) oxamides are square planar complexes that are either red, orange or green depending on the degree and type of substitution.[5,6] They are extremely stable complexes due, in part, to the highly unreactive oxamide portion of the macrocycle. Nickel(II) indoles, in contrast, are more susceptible to oxidative degradation due to the reactivity of the indole ring, leading to ring opening and ligand degradation.[7] The preparation of several nickel(II) oxamide and nickel(II) indole complexes, as well as related macrocyclic nickel(II) complexes, and their activity as catalysts in the epoxidation of alkenes is reported here.

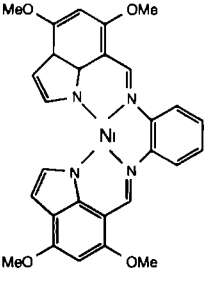
7.2 Results

7.2.1 Synthesis and catalytic activity of nickel(II) indole complexes

The nickel(II) indole complexes **1** and **2** were prepared according to Schemes 7.1 and 7.2, respectively.



1



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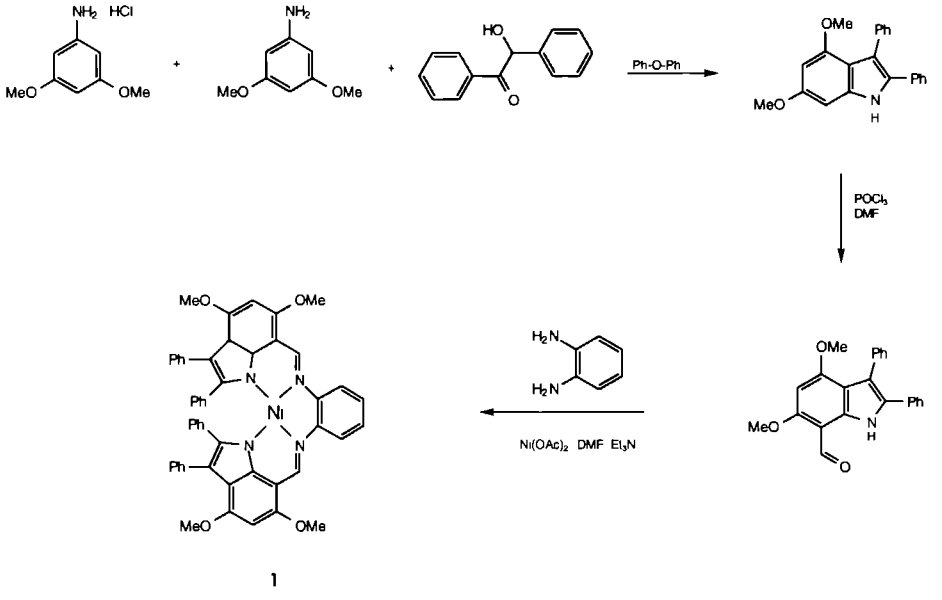
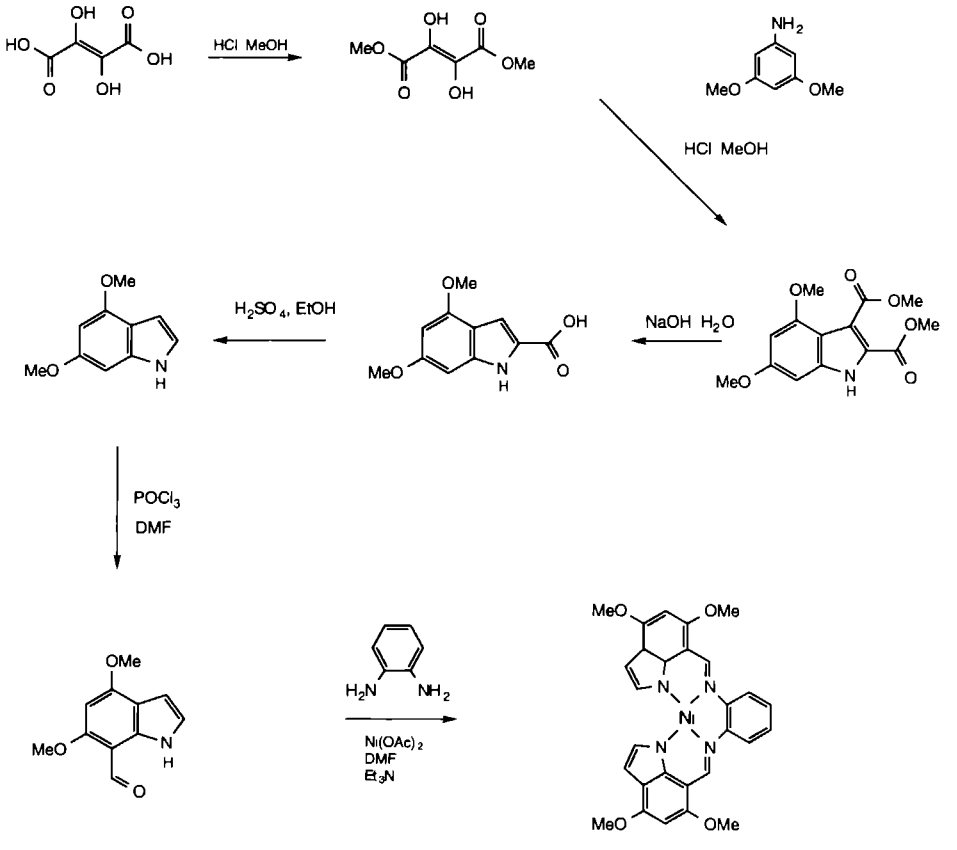
Scheme 7.1



In the first reaction step 3,5-dimethoxyaniline reacts with benzoine in a condensation and ring closure reaction to give 4,6-dimethoxy-2,3-diphenylidole in 12% yield. The yields for this reaction were not optimized and can most likely be improved. The substituted indole was subsequently formylated in a Vilsmeyer reaction to give 4,6-dimethoxy-2,3-diphenyl-7-formylindole. The formylation is directed to occur only at the 7-position due to the ortho-para methoxy directing groups. In the last step, the nickel(II) complex is formed in a template reaction with $Ni(OAc)_2$ and phenylene diamine in the presence of triethylamine. The Ni(II) indole **1** was isolated from the reaction mixture by filtration to give a deep red crystalline compound. Complex **2** was prepared as shown in Scheme 7.2.

Scheme 7.2



Dihydroxyfumaric acid was esterified in an acid-catalyzed reaction to give dimethyl dihydroxyfumarate. The 4,6-dimethoxyindole-2,3-dicarboxylic acid methylester was formed *via* a Bischler reaction from 3,5-dimethoxyaniline and the dimethyl dihydroxyfumarate in refluxing methanol Due to the presence of the methoxy groups the rate of the reaction is increased so that only the indole, and not the diaminomaleate,[8] is formed from the intermediate amino ketone The dimethoxy indole diester was hydrolyzed to give the 4,6-dimethoxylindole-2-carboxylic acid The subsequent decarboxylation step did not proceed smoothly and after several attempts, the synthesis of compound **2** was no longer attempted in our laboratory Compound **2** that was prepared elsewhere[9] was used further in epoxidation experiments

Like many of the oxamides, the indoles are deep red in color and have a square planar geometry around the nickel atom The X-ray structure of **2,** however, as reported in the

literature, is twisted, with one of the nitrogen atoms lying out of the plane[10] (Figure 7 1). The tetraphenyl substituted complex **1** is probably even more distorted due to the steric hindrance of the phenyl groups.

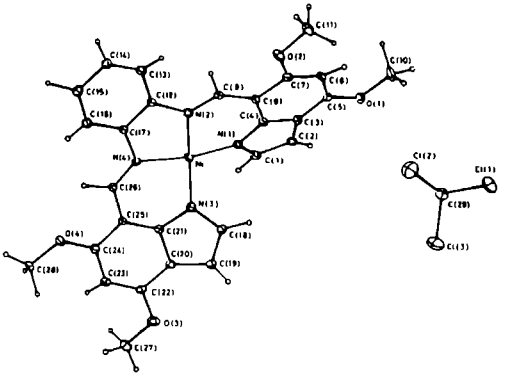


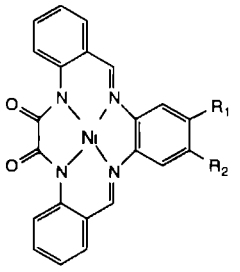
Figure 7.1 *X-ray structure of compound 2.*[10]

7.2.2 Epoxidation reactions with nickel(II) indole complexes 1 and 2

Epoxidation reactions with complexes **1** and **2** using α-pinene as a test substrate and molecular oxygen/aldehyde as the oxidant did not give any products. Complex **1** remained stable and was undegraded after several hours reaction time, whereas in reaction with complex **2,** the reaction solution turned black and the catalyst was degraded within one hour under normal reaction conditions. This rapid destruction of the catalyst is probably a result of the susceptibility of the indole ring to oxidative degradation. Due to their lack of reactivity and unstable nature under the epoxidation conditions, further investigation with complexes **1** and **2** was not carried out.

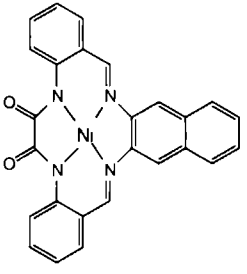
7.2.3 Synthesis and characterization of nickel(II) oxamide complexes

The Ni(II) oxamide complexes **3** - **8** shown in Chart 7. 2 were synthesized according to Scheme 7.3



Complex	R_1	R_2
3a	H	H
3b	OMe	H
3c	Cl	H
3d	NO_2	H
3e	Me	H
3f	NO_2	NH_2
3g	CH_3	CH_3
3h	$(CH_2)_3CH_3$	H
3i	COOH	H

3



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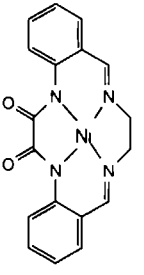

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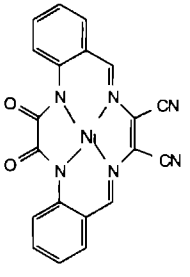

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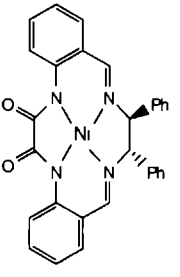

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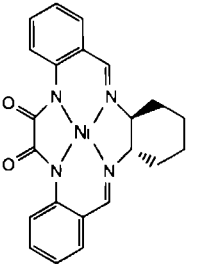

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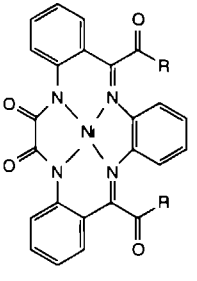
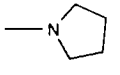


R = a OMe

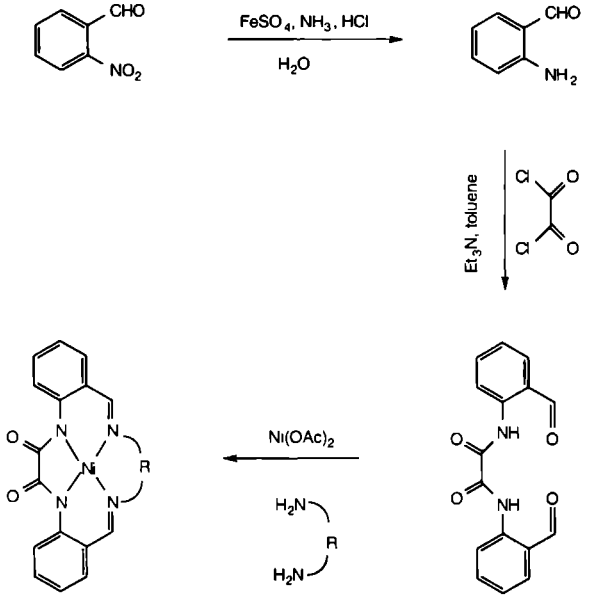
b NH_2

c 

9

Chart 7.2

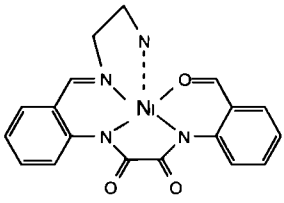
Scheme 7.3



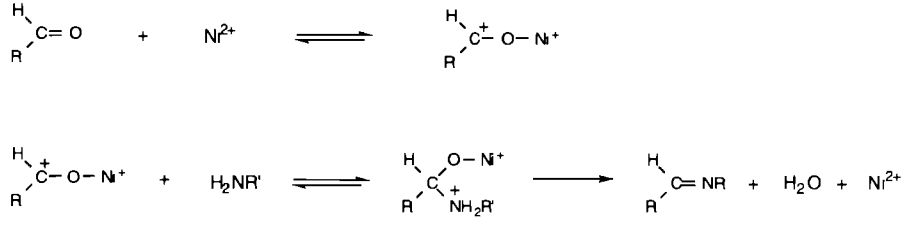
2-Nitrobenzaldehyde is an inexpensive starting material that was reduced to the aminobenzaldehyde in one step with $FeSO_4$ and ammonia Two equivalents of the aminobenzaldehyde were reacted with one equivalent of oxalylchloride to give the oxamide-bridged Schiff base. In a template reaction in the presence of nickel(II) ion, the oxamide-bridged Schiff base was reacted with an appropriate diamino compound to afford the corresponding nickel(II) macrocycle.

The metal-free macrocycle was not formed under these conditions when the reaction was carried out in the absence of nickel(II). The nickel ion exerts both a template influence and acts as a Lewis acid to effect the closure of the macrocyclic ligand[6] as shown in Scheme 7.4.

A



B



Scheme 7.4 *Template effect of the Ni^{2+} ion (A), and as a Lewis acid (B)*

Crystals of complex **3b**, suitable for x-ray diffraction, were grown by slow evaporation from DMSO The x-ray structure[11] of this complex is shown in Figure 7 2

A B

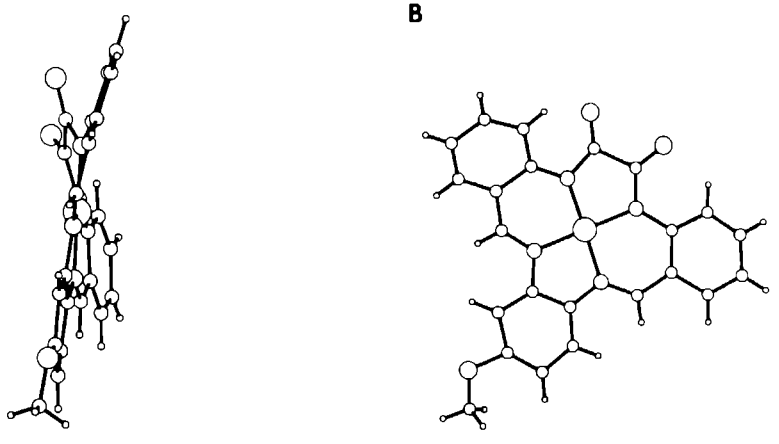


Figure 7.2 *X-ray structure of complex **3b** Side (A) and top (B) views*

Unlike complex **2**, which shows a twist of one of the coordinating nitrogen atoms out of the plane (see Figure 7.1), complex **3b** which is representative of all the nickel(II) oxamide complexes, is completely flat in its square planar geometry with all four coordinated nitrogen atoms lying in one plane. The methoxy group on the benzene ring is also lying in the same plane as the rest of the molecule.

7.2.4 Epoxidation reactions with nickel(II) oxamide complexes

Several modified nickel(II) oxamide catalysts were used in epoxidation reactions with α-pinene as test substrate and molecular oxygen/aldehyde as oxidant. The results are shown in Table 7.1.

Table 7.1 Epoxidation results of α-pinene with substituted nickel(II) oxamides[a]

Catalyst	Substitution	% Conversion	% Yield epoxide
3a	H	15	15
3b	OMe	4	4
3c	Cl	5	5
3d	NO_2	7	7
3e	Me	9	9
3f	NO_2/NH_2	6	5
3g	CH_3/CH_3	40	38
3h	$(CH_2)_3/CH_3$	0	0
3i	COOH	17	15
4	Naphthyl	26	26
5	Ethylene	100	85
6		12	12
7		100	92
8	Cyclohexyamethylene	100	84
9a	2 COOMe	94	88
9b	2 $CONH_2$	82	75
9c	2 Pyrroyl	71	67

[a]Reaction conditions: 0.5 mmol α-pinene, 1.5 mmol isobutyraldehyde, 1.0 mol % catalyst (respective to alkene), 5.0 cm^3 dichloromethane, 25 °C, 1.0 atmosphere O_2. Reaction time = 6h.

At low rates of conversion, the catalysts are 100% selective. It is only toward the end of the reaction, when the amount of substrate is low, that other products are formed in trace amounts. The majority of side-products are a result of rearrangements of the carbon skeleton of the α-pinene molecule. The poor conversion rates for complexes **3a-3i** are most likely due to their low solubility in dichloromethane. In addition to its ability to convert α-pinene to its corresponding epoxide, complex **5**, the most efficient and soluble of the complexes, was used to epoxidize several other unfunctionalized alkenes. These results are shown in Table 7.2.

Table 7.2 Epoxidation results with complex **5** as catalyst[a]

Alkene	% Conversion	% Yield epoxide
cis-Stilbene	47	41
trans-Stilbene	5	3
Norbornene	24	21
Cyclohexene	60	53
Camphene	52	41

[a]Reaction conditions: 0.5 mmol alkene, 1.5 mmol isobutyraldehyde, 1.0 mol % catalyst (respective to alkene), 5.0 cm^3 dichloromethane, 25 °C, 1.0 atmosphere O_2. Reaction time = 4h.

None of the alkenes listed in Table 7.2 is as reactive a substrate as is α-pinene. Longer reaction times are necessary for these substrates to be completely converted to their corresponding epoxides. The selectivity for epoxide is still respectable, however, and using a higher concentration of catalyst would most likely give epoxide yields and selectivities that approach those when found using α-pinene as substrate. Except for norbornene and cyclohexene, which gave much lower and slightly higher epoxide yields, respectively, than was the case using bis-(*p-t*-butylbenzyl-2,4-pentanediono)-Ni(II) (complex **4**, Chapter 5) as catalyst. The other substrates gave comparable epoxide yields with both catalysts.

The stability of selected catalysts was followed by UV-vis spectroscopy. In the presence of a sufficient quantity of substrate, the catalysts remained stable throughout the reaction. In the absence of substrate, however, and when more than 70% of the substrate had been converted to product, the catalyst was quickly degraded (Figure 7.3).

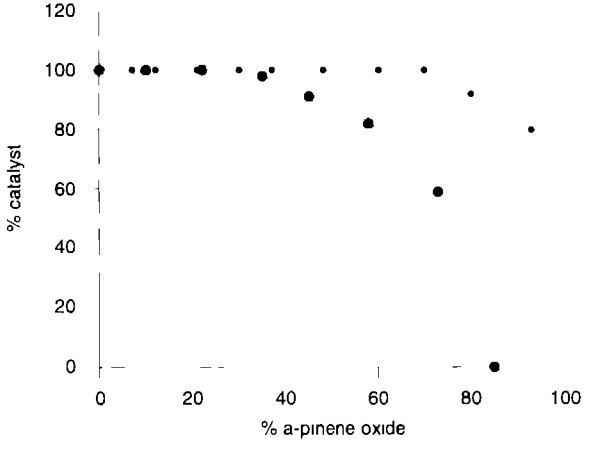
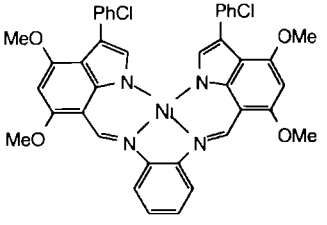


Figure 7.3 *Stability of complexes 5(◊), 7(•), and 8(●)under standard epoxidation conditions (see Table 7.2).*

Of the three catalysts depicted in Figure 7.3, the most stable is the diphenyl substituted oxamide, complex **7,** which produced a yield of 93% α-pinene epoxide. The least stable of the catalysts is the less rigid complex **5** which, although quickly degraded after substrate conversion is complete, was able to give a yield of 85% epoxide.

7.2.5 Other related nickel(II) macrocycles

In addition to the nickel(II) indoles and nickel(II) oxamides described above, several analogous nickel(II) macrocycles were examined for their catalytic activity. These complexes are depicted in Chart 7.3.



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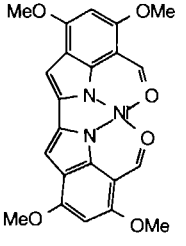

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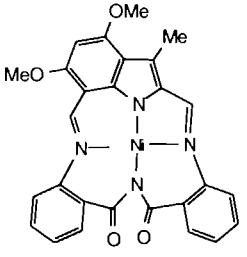

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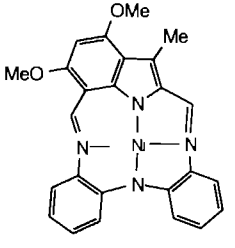

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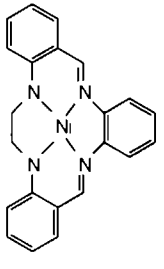

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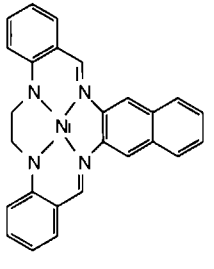

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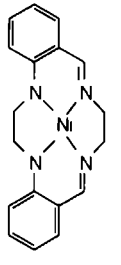

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Chart 7.3

Complexes **10-16** were tested for their ability to convert α-pinene to its corresponding epoxide under the standard reaction conditions. All of these complexes proved to be inactive as catalysts. It is interesting to note that small differences in the macrocycle can have a profound effect on the ability of the nickel(II) complex to catalyze the epoxidation of a reactive substrate such as α-pinene. Complexes **10-13** contain an indole ring which is probably subjected to oxidative degradation during the course of the reaction. More importantly, however, the electronic and steric character of the macrocycle surrounding the nickel ion in these complexes is not able to stablize the nickel-peroxo complex (see Chapter 6) that is the putative oxygen transfer species. Complexes **14-16** are analogous to complexes **3-9** except that they are missing the oxamide bridge. This part of the ligand appears to be important in stabilizing the catalyst and enhancing its activity, since removal of this oxamide bridge completely inactivates the catalyst.

7.2.6 Other oxygen atom donors for epoxidation

Although somewhat outside the scope of this thesis which concentrates on the use of molecular oxygen as the terminal oxidant in the epoxidation of alkenes, we thought it would be of interest to compare the activity of the nickel(II) oxamide catalysts with that of other nickel(II) macrocycles such as salen, salophen, cyclam, and porphyrin which have been reported in the literature to epoxidize a variety of alkenes in conjunction with such oxygen atom donors as sodium hypochlorite and iodosylbenzene.[12-15] Selected results with some nickel(II) oxamide complexes in combination with NaOCl or iodosylbenzene are shown in Tables 7 3 and 7.4.

Table 7.3 Epoxidation results with iodosylbenzene[a]

Complex	% Conversion	% Yield epoxide
3a	1 5	1 5
5	1 5	1 5
7	1 5	1 5
8	1 5	1 5

[a]Reaction conditions: 0 5 mmol dm^{-3} α-pinene, 0 25 mmol dm^{-3} iodosylbenzene, 1 0 mol % catalyst, 5 0 cm^3 dichloromethane, 25 °C, N_2 atmosphere Reaction time = 6h

Table 7.4 Epoxidation results with sodium hypochlorite (two-phase conditions)[a]

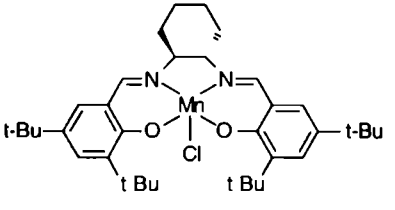
Complex	% Conversion	% Yield epoxide
3a	38	19
5	63	22
7	16	11
8	27	16

[a]Reaction conditions 0 5 mmol dm^{-3} α-pinene, 1 0 mol% catalyst, 015 mmol benzyltributylammonium chloride, 5 0 cm^3 dicloromethane , 5 0 cm^3 NaOCl (household bleach), 25 °C, N_2 atomsphere Reaction time = 3 h A phase transfer catalyst (benzyltributylammonium chloride) was added to facilitate transfer between the aqueous and organic phases

Addition of iodosylbenzene to the reaction mixture did not result in a color change of the catalyst This is in contrast with what has been reported using Mn(III) salen complexes in conjunction with iodosylbenzene, where a color change indicated coordination of the iodosylbenzene to the Mn(III) ion [15] Although our reactions were not followed spectroscopically, we assume that the catalysts remain intact throughout the course of the reaction due to a lack of color change or bleaching of the solution Compared with results of nickel(II) complexes and iodosylbenzene reported in the literature,[14 15] the nickel(II) oxamides are not very reactive with iodosylbenzene as the oxygen donor, giving yields of less than 2% for α-pinene, although other more electron-rich alkenes may be better substrates under these conditions Epoxidation of α pinene with sodium hypochlorite, however, showed results comparable to those previously reported in the literature with nickel(II) salen, nickel(II) cyclam and nickel(II) porphyrins Studies by Burrows and co workers[12 13] using Ni(II) salen and Ni(II) cyclam complexes showed a lower reactivity using NaOCl than did the Ni(II) oxamide compounds under similar reaction conditions The Ni(II) oxamide complexes showed on average a four-fold increase in epoxide yields

7.2.7 Chiral nickel(II) oxamide catalysts

Chiral nickel oxamides **7** and **8** were prepared with the aim of achieving asymmetric induction during the reaction in order to give an enantiomeric excess of chiral epoxide products from pro-chiral alkenes The oxamide macrocycle satisfies the requirements of rigidity and non-kinetic lability for a chiral catalyst [3] This rigidity and non-lability was lacking in the chiral β diketonate ligands described in Chapter 5 Due to the similarity of the oxamide macrocycle to the Jacobsen catalyst[3 17] (**E**) we hoped to achieve similar enantioselectivities, if not with the nickel(II) complex, than with a manganese(III) containing chiral oxamide



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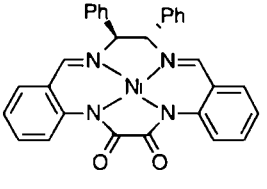

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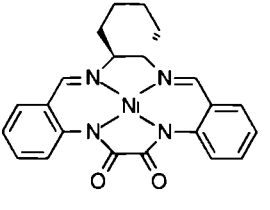

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Epoxidation reactions were carried out with *trans*-β-methylstyrene and *cis*-β-methyl styrene in dichloromethane at 25 °C and at 0 °C The results are shown in Table 7 5

Table 7.5 Epoxidation results with chiral catalysts **7**and **8**[a]

Catalyst	Alkene	Temp °C	% Yield epoxide	% ee
7	*trans*-β-Methylstyrene	25	28	3
7	*trans*-β Methylstyrene	0	3	1
8	*trans*-β-Methylstyrene	25	47	4
8	*trans* β-Methylstyrene	0	3	1
3a	*trans*-β-Methylstyrene	25	11	1
7	*cis*-β Methylstyrene	25	36	3
8	*cis*-β-Methylstyrene	25	51	3

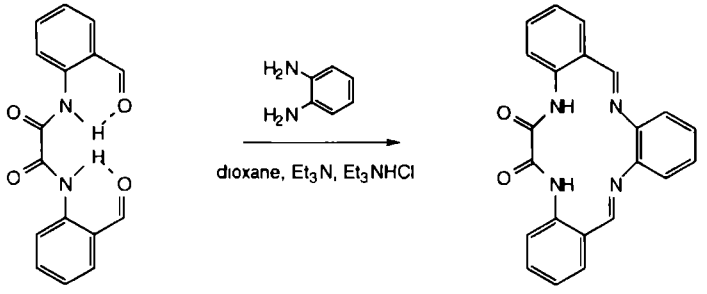
[a]Reaction conditions 0 5 mmol alkene, 1 5 mmol isobutyraldehyde, 1 0 mol % catalyst (respective to alkene) 5 0 cm^3 dichloromethane, 1 0 atmosphere O_2 Reaction time = 6h

No appreciable enantioselectivity in the products was found in using *trans*-β-methyl styrene and *cis*-β-methyl styrene alkenes This result is in keeping with the radical nature of the oxygen transfer step for this reaction as described in Chapter 6, in which rotation around the carbon-carbon bond of the alkene occurs during the oxygen insertion step

7.2.8 Synthesis of the metal-free oxamide ligand

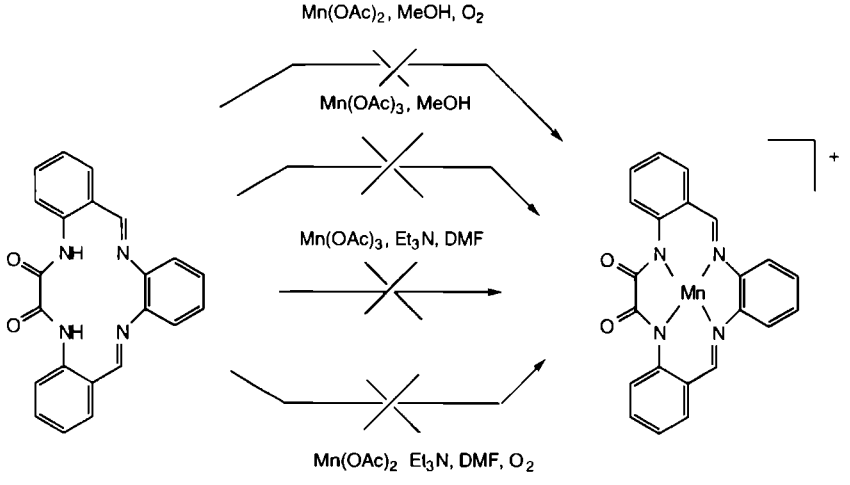
Because of the poor ee's produced using the chiral nickel(II) oxamide derivatives **7** and **8**, we wished to prepare the manganese(III) chiral complexes that are directly analogous to the Jacobsen catalyst After several unsuccessful attempts, we discovered that the free ligand of complex **3a** could be successfully prepared using very dry dioxane[18] (Scheme 7 5) In the initial attempts, the presence of water in the solvent appeared to catalyze intermolecular polymerization reactions between the diamines and the aldehyde portion of oxamide-bridged Schiff base [19]

Scheme 7.5



With the pure oxamide ligand in hand, we attempted to insert a Mn(III) ion into the macrocycle without success The various approaches that were used are summarized in Scheme 7 6

Scheme 7.6



Warming the free ligand with manganese(II) acetate tetrahydrate in air resulted in the recovery of the ligand and free Mn(III) acetate salt Attempts to directly insert the manganese(III) ion into the macrocycle by refluxing the ligand in the presence of mangansese(III) acetate tetrahydrate were also not successful

Note during the preparation of this manuscript it was discovered that allowing both ligand and $Mn(II)OAc_2\,4H_2O$ to sit at room temperature in DMF/methanol solution for one week, resulted

in the formation of the Mn(III) oxamide complex Further investigations on the catalytic ability of this complex and the synthesis of the chiral Mn(III) oxamide complexes were not carried out due to time constraints

7.3 Discussion

Although slower than the bis-(3-alkyl-2,4-pentanediono)-Ni(II) catalysts at converting alkene to epoxide, the nickel(II) oxamide catalysts gave very good yields of α-pinene epoxide in the presence of molecular oxygen and isobutyraldehyde A major factor in their lower reactivity is the relative insolubility of the nickel(II) oxamide complexes in most organic solvents Neither of the two indole complexes yielded any epoxide, nor were the nickel(II) indole complexes able to convert α-pinene into any oxidation products The tetraphenyl substituted indole **1** remained stable under the reaction conditions, but access to the nickel site was probably hindered by the presence of the overlapping phenyl rings The non-substituted indole complex **2** was oxidized during the reaction, probably as a result of the highly activated dimethoxy substituted benzene rings of the indole portion of the catalyst As a result of this lack of activity we did not further investigate the indole complexes

Complexes **5**, **7**, **8**, and **9a** gave the highest yields of α-pinene epoxide under standard reaction conditions Conversion of α-pinene with each of these catalysts was 100% with epoxide yields ranging from 85 - 92% Complex **5** was also efficient at converting a variety of other alkenes to their corresponding epoxides, including, *cis*- and *trans*-stilbene, norbornene, camphene, and cyclohexene Complex **5** gave lower epoxide yields for norbornene than did bis-(3-*p*-*t*-butylbenzyl-2,4-pentanediono)-Ni(II), but higher yields with *cis*-stilbene under identical reaction conditions

The oxamide bridge portion of the molecule appears to be an important factor in the reactivity of the nickel(II) oxamide complexes as catalysts When this bridging portion is absent as in complexes **14-16**, the molecule is rendered inactive as a catalyst The absence of the rigid oxamide bridge with its sp^2 hybridized carbons may allow for a more tetrahedral geometry around the nickel(II) ion causing it to be unfavorable in stabilizing the proposed metal-peroxo active species (see Chapter 6) Like the Ni(II) indole complexes **1** and **2**, complexes **10** and **11** which are also built from indole groups, were inactive as catalysts

In order to compare the activity of the nickel(II) oxamide catalysts with analogous catalysts reported in the literature, selected nickel(II) oxamide complexes were tested for their ability to epoxidize α-pinene with either iodosylbenzene of sodium hypochlorite as oxygen atom donor The nickel(II) oxamide complexes **3a**, **5**, **7** and **8** were not very efficient at converting α-pinene to its corresponding epoxide, although more electron-rich alkenes, which were not tested, may prove to be more reactive Using NaOCl as the oxygen atom donor gave yields of up to 22% with the same catalysts although the selectivity under these conditions was quite low

Chiral nickel complexes **7** and **8** which are analogous to the chiral manganese(III) Jacobsen catalysts[3] were used in an attempt to induce asymmetric induction during the epoxidation of such pro-chiral alkenes as *cis*-β-methylstyrene and *trans*-β-methylstyrene Jacobsen's chiral manganese catalyst can give ee's as high as 90% for selected *cis*-alkenes Complexes **7** and **8** gave no significant ee's with either the *trans*- or the *cis*- isomer of β-methylstyrene most likely

as a result of the radical nature of the oxygen transfer process (See Chapters 2 and 6) which allows for rotation around the carbon-carbon bond Further efforts for preparing and testing the chiral manganse(III) oxamide complexes for catalytic ability and the ability to induce asymmetry during the reaction are in progress, and will hopefully lead to more selective and more stable manganese(III) chiral catalysts than those already described in the literature [3,18,19]

7.4 Experimental

Materials. Unless otherwise noted all reagents were purchased from Aldrich and used without further purification Dichloromethane was distilled over calcium chloride and stored over 4 Å molecular sieves DMF was distilled under reduced pressure over magnesium sulfate and stored over 4 Å molecular sieves Toluene and hexane were distilled over sodium metal/ benzophenone and stored over 4 Å molecular sieves Triethylamine was distilled and stored over potassium hydroxide 1,2-Phenylenediamine was recrystallized before use from toluene α-Pinene was purified by column chromatography (dichloromethane, basic alumina) and stored at -18 °C Isobutyraldehyde was distilled before use and stored at -18 °C

Instrumentation. ^{1}H-NMR spectra were taken on a Bruker AC 100 MHz-spectrometer Chemical shifts (δ) are given in ppm downfield from TMS IR spectra were taken on a Perkin Elmer 1720-X Infra red Fourier Transform spectrometer or a Bio-rad TFS-25 spectrometer GC-analyses were carried out on a Varian 3700 gas chromatograph with a flame ionization detector, coupled to a Hewlett Packard 3395 integrator HPLC-analyses were carried out on a LKB Bromma 2150 HPLC ramp and 2152 HPLC controller, coupled to a LKB Bromma 2221 integrator (column Chiralpak OD or AD, eluent = hexane propanol, 99 1, v/v) UV-visible spectra were taken on a Perkin Elmer Lambda 5 spectrometer Elemental analyses were determined with a Carlo Erba Ea 1108 Mass spectra were taken on a VG 7060 E spectrometer The crystal structure in Figure 7 2 was determined at 60 °C using the program packet DIRDIF The solution was refined using an automatic Patterson interpretation technique (PATTY) Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected

Syntheses

2-Aminobenzaldehyde. A 500 ml three-necked round bottom flask was charged with 150 cm^3 water, 87 5 g (0 31 mol) iron sulfate heptahydrate, 0 42 cm^3 concentrated hydrochloric acie, and 5 0 g (0 033 mol) 2 nitrobenzaldehyde The reaction mixture was stirred and warmed until the temperature reached 90 °C At that point, 21 0 cm^3 of an aqueous 25% ammonia solution was added followed by three portions of 8 0 cm^3 of an aqueous 25% ammonia solution added in intervals of two min After the addition of the last portion of ammonia solution, stirring and warming were stopped and the reaction mixture was steam distilled The distillate was saturated with sodium chloride and this solution was stirred at 5 °C, until the product was precipitated The 2-aminobenzaldehyde was filtered and dried in air Yield 2 84 g (71%) of flat, pale yellow crystals ^{1}H NMR (100 MHz, $CDCl_3$) δ 9 88 (s, 1H, COOH), 7 54-7 24 (m 2H, ArH), 6 83-6 61 (m, 2H, ArH), 6 12 (br s, 1H, NH)

***N,N'*-(Di-*o*-formylphenyl)oxanilide** To a solution of 1 90 g (16 mmol) 2-aminobenzaldehyde in 40 cm^3 toluene was added 0 69 cm^3 (8 0 mmol) oxalylchloride and 2 19 cm^3 (16 mmol) triethylamine The reaction mixture was stirred for 3 h at 20 °C The

solid material formed was filtered and suspended in 400 cm^3 saturated aqueoussodium carbonate solution, stirred, filtered and washed with water and dried The product was re-crystallized from a large volume of acetic acid to give a white powder Yield 1 14 g (49%) ^{1}H-NMR was not taken due to poor solubility IR (KBr) ν_{max} (cm^{-1}) = 3204, 2845, 2765 (NH), 1683, 1604, 1584, 1519 (C=O), Anal calculated for $C_{16}H_{12}O_4N_2$ C 64 86, H 4 08, N 9 45, found C 64 73, H 3 94, N, 9 34, M p 313 °C

Nickel(II) complexes 3a, 3c, 7, 8. A mixture of *N,N'*-(di-*o*-formylphenyl)oxanilide (0 5 mmol), nickel acetate tetrahydrate (0 5 mmol), diamine (0 5 mmol), and triethylamine (1 0 mmol) was stirred in DMF under a nitrogen atmosphere at 120 °C After a reaction time of 24-30 hours, the reaction mixture was cooled and ice cold methanol was added to the reaction flask The nickel(II) complex precipitated out of the solution and was collected by filtration The filtrate was washed with ice cold methanol and dried Yield **3a**, 88% purple crystals IR (KBr) ν_{max} (cm^{-1}) = 1669, 1653 (C=O), 1617 (C=N), UV-vis (CH_2Cl_2) λ_{max} 375 nm (ε = 26618 dm^3 mol^{-1} cm^{-1}), FAB-MS *m/z* 425 ([M+H]$^+$), anal calc for $C_{22}H_{14}N_4O_2Ni$ C 62 16, H 3 32, N 13 18, found C 62 15, H 3 18, N 12 99, M p, > 350 °C

3c, 63% red/brown powder IR (KBr) ν_{max} (cm^{-1}) = 1670, 1650 (C=O), 1615 (C=N), FAB MS *m/z* 455 ([M+H]$^+$), anal calc for $C_{22}H_{13}N_4O_2ClNi$ C 57 51, H 2 85, N 12 19, found C 57 31, H 2 85, N 11 87 M p > 350 °C

7, 62% orange powder ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8,87 (d, 2H, ArH3, J = 9 Hz) 7 75 (d, 4H, ArH10, J = 7 Hz), 6 85 (t, 2H, ArH5, J = 7 Hz), 4 75 (s, 2H, CH8), IR (KBr) ν_{max} (cm^{-1}) = 1653, 1629 (C=O), Anal Calc for $C_{30}H_{22}O_2N_4Ni$ C 68 09, H 4 19, N 10 59, found C 67 62, H 4 05, N 10 37 M p > 350 °C

8, 84% orange powder IR (KBr) ν_{max} (cm^{-1}) = 1643, 1628 (C=O), UV-vis (CH_2Cl_2) λ_{max} 410 nm (ε = 9785 dm^3 mol^{-1} cm^{-1}), FAB-MS *m/z* 431 ([M+H]$^+$) Anal calc for $C_{22}H_{20}N_4O_2Ni$ C 61 29, H 4 68, N 13 00, found C 60 73, H 4 53, N 12 66 M p > 350 °C

Nickel(II) complex 5. A mixture of 100mg (0 34 mmol) *N,N'*-(di-*o* formylphenyl) oxanilide , 84 mg (0 34 mmol) nickel(II) acetate tetrahydrate and 68 ml (1 0 mmol) 1,2 ethylenediamine was stirred in DMF under a nitrogen atmosphere at 120 °C After a reaction time of 25 hrs , the reaction mixture was cooled and ice cold methanol was added The orange/brown precipitate was filtered and purified by column chromatography ($CHCl_3$ MeOH Et_3N, 89 10 1, v/v, silicagel) and recrystallized from DMF/ methanol Yield 20 mg (16%) orange needles IR (KBr) ν_{max} (cm^{-1}) = 1653, 1624 (C=O), UV-vis (CH_2Cl_2) λ_{max} 411 nm (ε = 7559 dm^3 mol^{-1} cm^{-1}) , FAB MS *m/z* 377 ([M+H]$^+$) Anal calc for $C_{18}H_{14}N_4O_2Ni$ C 57 34, H 3 74, N 14 86, found C 57 15, H 3 83, N 14 45 M p > 350 °C

Nickel(II) complex 3b. A mixture of 40 mg (0 14 mmol) *N,N'*-(di-o-formylphenyl)oxanilide, 34 mg (0 14 mmol) nickel(II) acetate tetrahydrate, 29 mg (0 14 mmol) 4-methoxy-1,2-phenylenediamine hydrochloride, and 75 cm^3 (0 54 mmol) triethlamine was stirred in DMF under a nitrogen atmosphere at 120 °C After a reaction time of 24 hours the reaction mixture was cooled and ice cold methanol was added to precipitate the product A light brown precipitate was filtered off and the solvent removed from the deep red filtrate Deep red crystals formed and these were filtered and washed with cold methanol Yield 30 mg (49%) dark red crystals IR (KBr) ν_{max} (cm^{-1}) = 1659, 1617 (C=O), 1259 (C-O-C) FAB-MS *m/z* 455 ([M+H]$^+$) Anal Calc for $C_{23}H_{16}N_4O_3Ni$ C 60 70, H 3 54, N 12 31, found C 58 50, H 3 54, N 11 56 M p 320 °C

2,3-Diphenyl-4,6-dimethoxyindole. A mixture of 2.14 g (14.0 mmol) 3,5-dimethoxyaniline, 1.48 g (7.0 mmol) (±) benzoine, and 1.33 g (7.0 mmol) 3,5-dimethoxyalinium hydrochloride in 10 cm^3 of diphenylether was stirred for 2 hrs at 140 °C. The 4,6-dimethoxy-2,3-diphenylindole precipitated from the cooled reaction mixture and purified by column chromatography (ethyl acetate : hexane, 1 : 5, v/v, silica gel). The light yellow fraction contained the desired product. The solvent was removed from this fraction and the residue was recrystallized from chloroform/petroleum-ether (60 - 80 °C) Yield: 0.28 g (12%) of a pale gray powder. ^{1}H-NMR ($CDCl_3$): δ 8.13 (br s, 1H, NH), 7.24-7.38 (m, 10H, ArH), 6 53 (d, 1H, H5, J = 2 Hz), 6.22 (d, 1H, H7, J= 2 Hz), 3.87, 3 67 (s, 6H, OCH_3).

2,3-Diphenyl-4,6-dimethoxy-7-formylindole. To a stirring solution of 0.26 g (0.80 mmol) 4,6-dimethoxy-2,3-diphenylindole in 1.0 cm^3 DMF at 0 °C was added dropwise 74 cm^3 (0 80 mmol) phosphorylchloride. The reaction mixture was stirred for 1 hour at 0 °C. Cold water (4 cm^3) was added to the reaction mixture and this solution was made strongly basic with 10% NaOH solution. After allowing the solution to stir at room temperature for 30 minutes the solid material was filtered, washed with water and dried. Yield: 0.24 g (85%) of a yellow powder. ^{1}H-NMR (DMSO-d_6): δ 10.99 (br s, 1H, NH), 10.43 (s, 1H, HCO), 7.37 (m, 10H, ArH), 6.55 (s, 1H, H5), 4 11, 3.90 (s, 6H, OCH_3).

Nickel(II) indole complex 1. A mixture of 0 10 g (0.28 mmol) 4,6-dimethoxy-2,3-diphenyl-7-formylindole, 15 mg (0 14 mmol) 1,2-phenylenediamine, 35 mg (0.14 mmol) nickel(II) acetate tetrahydrate and 39 cm^3 (0.28 mmol) triethylamine in DMF was stirred for 17 hours at 120 °C under a nitrogen atmosphere. The solvent was removed from the reaction mixture and the residue was recrystallized from chloroform/methanol. Yield: 63 mg (53%) of a deep red powder. ^{1}H-NMR (400 MHz, $CDCl_3$). δ 8.80 (s, 2H, N=CH), 7 72-6.66 (m, 24H, ArH), 5.91 (s, 2H, ArH5), 4.04 and 3.67 (2s, 12H, OCH_3); IR (KBr). ν_{max} (cm^{-1}) = 1595, 1579 (C=N), 1259 (OCH3); FAB-MS: *m/z* 843 ($[M+H]^+$). Anal calc. for $C_{52}H_{40}N_4Ni.H_2O$, C 72.49, H 4.91, N 6 50; found: C 72.42, H 4.93, N 6.16. M p. decays > 200 °C

Dimethyl dihydroxyfumarate. To a solution of 15.0 g (0 10 mol) dihydroxyfumaric acid in 80 cm^3 methanol in a three-neck round bottom flask was added 20.3 g (0.17 mol) anhydrous magnesium sulfate. The reaction mixture was stirred and cooled to 0 °C Hydrogen chloride gas was bubbled through the reaction for 4 hrs. The reaction was allowed to stand at room temperature for 3 days after which the solid material was filtered, rinsed with methanol and added to 200 cm^3 cold water. The product was filtered and washed with cold water to remove any remaining acid and sulfate. Yield: 9.67 g (54%) of a white powder. ^{1}H-NMR ($CDCl_3$) δ 9 50 (s, 2H, OH), 3.97 (s, 6H, CH_3).

Dimethyl 4,6-dimethoxyindol-2,3-dicarboxylate. A solution of 5.0 g (33 mmol) 3,5-dimethoxyaniline in 50 cm^3 methanol was added dropwise to a refluxing solution of 6.3 g (36 mmol) dimethyl dihydroxyfumarate and 13 drops of 37% HCl in 125 methanol. The reaction mixture was refluxed for 16 hrs and then cooled The precipitate was filtered, rinsed with cold methanol and dried. Yield: 7.63 g (80%) of a pale cream powder. ^{1}H-NMR ($CDCl_3$). δ 8.95 (br s, 1H, NH), 6.39 (d, 1H, H5, J = 2 Hz), 6.19 (d, 1H, H7, J = 2 Hz), 3 97, 3.90, 3.86, 3.82 (s, 12 H, OCH_3).

4,6-Dimethoxyindol-2-carboxylic acid. A suspension of 3.0 g (10 mmol) dimethyl 4,6-dimethoxy-2.3-dicarboxylate in 70 cm^3 of aqueous 5.0 N NaOH solution was refluxed for 16 hrs The reaction mixture was cooled, diluted with 180 cm^3 of water and acidified with 3.0 N

HCl. The precipitate was filtered, washed with water and dried. Yield: undetermined ^{1}H-NMR (DMSO-d_6): δ 11.77 (br s, 1H, NH), 7.13 (d, 1H, H5, J = 2 Hz), 6 63 (s, 1H, H3), 6 34 (d, 1H, H7, J = 2 Hz), 4.00, 3.92 (s, 6H, OCH_3).

Metal-free oxamide ligand. *N,N'*-(di-*o*-formylphenyl)oxanilide (0.34 mmol, 0.10 g) was suspended in 8.0 cm^3 dry dioxane. This suspension was stirred under a nitrogen atmosphere 1,2-Phenylenediamine (0.34 mmol, 37 mg) and 50 mg triethylamine hydrochloride and 67 mm^3 triethylamine were added. The reaction mixture was refluxed under a nitrogen atmosphere, during which time the color changed from white to yellow. After 18 hrs, the reaction mixture was allowed to cool, and was filtered over a glass frit. The residue was washed several times with ethylacetate and dried. Yield. 72 mg (58%) of a yellow powder ^{1}H-NMR ($CDCl_3$): δ 13 51 (s, 2H, NH), 8.67 (s, 2H, CH7), 7.93 (d, 2H, ArH6, J = 8 Hz), 7 52 (d, 2H, ArH3, J = 8 Hz), 7.34-7.32 and 7 11-7.08 (2m, 4H, ArH4, ArH5), 7 03 and 6.79 (2t, 4H, ArH9, ArH10, J = 8 Hz); IR (KBr): νmax (cm^{-1}) = 3435, 3345 (NH), 1674 (C=O), 1606 (C=N); FAB-MS: *m/z* 367 ([M-H$^+$]). Anal calc. for $C_{22}H_{16}N_4O_2$. C 71 73, H 4.38, N 15.21; found: C 71.96, H 4.36, N 15.00 M.p. >350 °C.

Complexes 3d, 3e, 3f, 3g, 3h, 3i, 4, 6, 10-16, and the ligands for complexes 9a, 9b, and 9c. These compounds were the kind gift of Prof. David St C Black of the University of New South Wales, Sydney, Australia.

Epoxidation Reactions.

Epoxidation of alkenes with molecular oxygen in the presence of isobutyraldehyde

A Schlenck tube (10 cm x 2 cm) was charged with 5.0 cm^3 dichloromethane, 80 mm^3 (0 5 mmol) α-pinene, 136 mm^3 (1 5 mmol) isobutyraldehyde and 1.0 mol % (respective to the alkene) catalyst. The Schlenk tube was evacuated and then filled with O_2. The reaction mixture was stirred at 1000 rpm at 25 °C under 1.0 atomsphere O_2 for 6 hours at which time the reaction was stopped, an internal standard was added (*o*-dichlorobenzene) and the mixture analyzed by GLC. The stability of the catalysts was determined by measuring an aliquot from the reaction mixture at varying intervals by UV-vis spectroscopy.

Epoxidation of α-pinene with iodosylbenzene

A Schlenck tube (10 cm x 2 cm) was charged with 5.0 cm^3 dichloromethane and to this was added 80 mm^3 (0 5 mmol) α-pinene, 55 mg (0.25 mmol) iodosylbenzene and 5 0 x 10^{-3} mmol (1 mol %) catalyst. The Schlenk tube was fitted with a septum, evacuated and filled with 1 0 atmosphere N_2 The reaction mixture was stirred magnetically at room temperature After 6 hrs, the stirring was stopped and the reaction mixture was analyzed by GLC

Epoxidation of α-pinene with sodium hypochlorite

A Schlenk tube (10 cm x 2 cm) was charged with 5.0 cm^3 dichloromethane, 80 mm^3 (0 5 mmol) α-pinene, 6.8 mg (0.019 mmol) benzyltributylammonium bromide (phase transfer catalyst), and 5 0 x 10^{-3} mmol (1 mol %) catalyst. Layered on top of this solution was 5 0 cm^3 of a sodium hypochlorite solution (household bleach). The reaction mixture was stirred vigorously at room temperature. After 3 hrs the stirring was stopped and 0 5 cm^3 of a 0 05 mol.dm^{-3} stock solution of *o*-dichlorobenzene in dichloromethane was added to 0 5 cm^3 of the organic phase of the reaction mixture. An aliquot of this solution was analyzed by GLC

7.5 References

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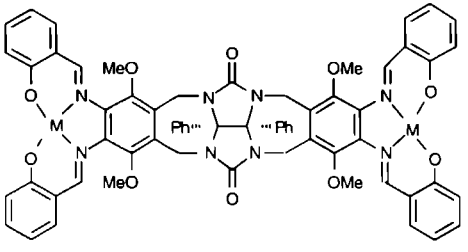
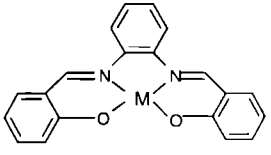
Nickel(II) and Manganese(III) Square Planar Catalysts Functionalized with a Binding Site

8.1 Introduction

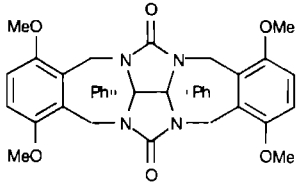
One way to achieve enantio- or shape-selectivity in epoxidation reactions is to functionalize a catalytic center with a receptor-like moiety that is capable of discriminating between different substrates or different faces of a substrate.[1-7] A synthetic receptor would bind a particular molecule and orient it in such a way that it is close to the catalytically active metal center. We designed a complex (**1**) in which a catalytically active part, a nickel(II) or manganese(III) salen moiety (**2**), is attached to the walls of synthetic clip **3.** This synthetic clip is capable of binding a variety of substituted dihydroxybenzenes with binding constants ranging from 3,000 $dm^3\ mol^{-1}$ (for 1,3-dihydroxybenzene) to 35,000 $dm^3.mol^{-1}$ (methyl-3,5-dihydroxybenzoate) in $CDCl_3$.[8,9]



1 **a**, M = 2H
b, M = Ni(II)
c, M = Mn(III)



2 **a**, M = 2H
b, M = Ni(II)
c, M = Mn(III)



3

Compound **3** has been used previously in our laboratory as the basis of synthetic enzyme-type catalysts that, when modified with pyrazole ligands for copper ions,[10] or a rhodium-phosphite or phosphine moiety[11] are able to selectively catalyze the oxidation of dihydroxy substituted aromatic aldehydes and the hydrogenation of dihydroxyaryl alkenes, respectively

Nickel(II) salophen **2b** is capable of epoxidizing alkenes using NaOCl, or molecular oxygen/aldehyde as the oxidizing agent. Manganese(III) salophen **2c** is able to epoxidize alkenes using NaOCl or iodosylbenzene as the oxidizing agent. Molecular clip **3** is able to bind a variety of dihydroxy benzenes as depicted in Figure 8.1. A dihydroxybenzene modified with a double bond, such as 1-allyl-3,5-dihydroxybenzene should show higher epoxidation rates with complex **1** due its ability to bind in the cleft that is close to the metal-containing catalytic center, bringing the substrate alkene closer to the catalytic center where oxygen transfer occurs.

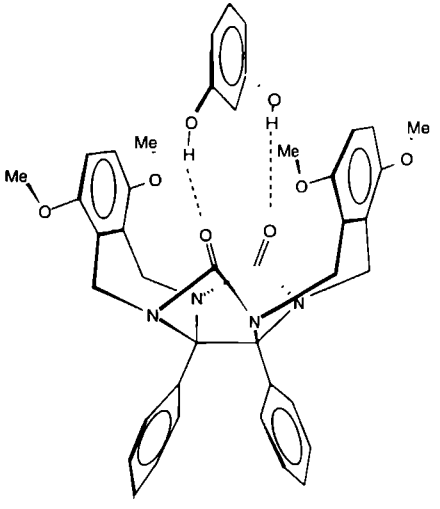


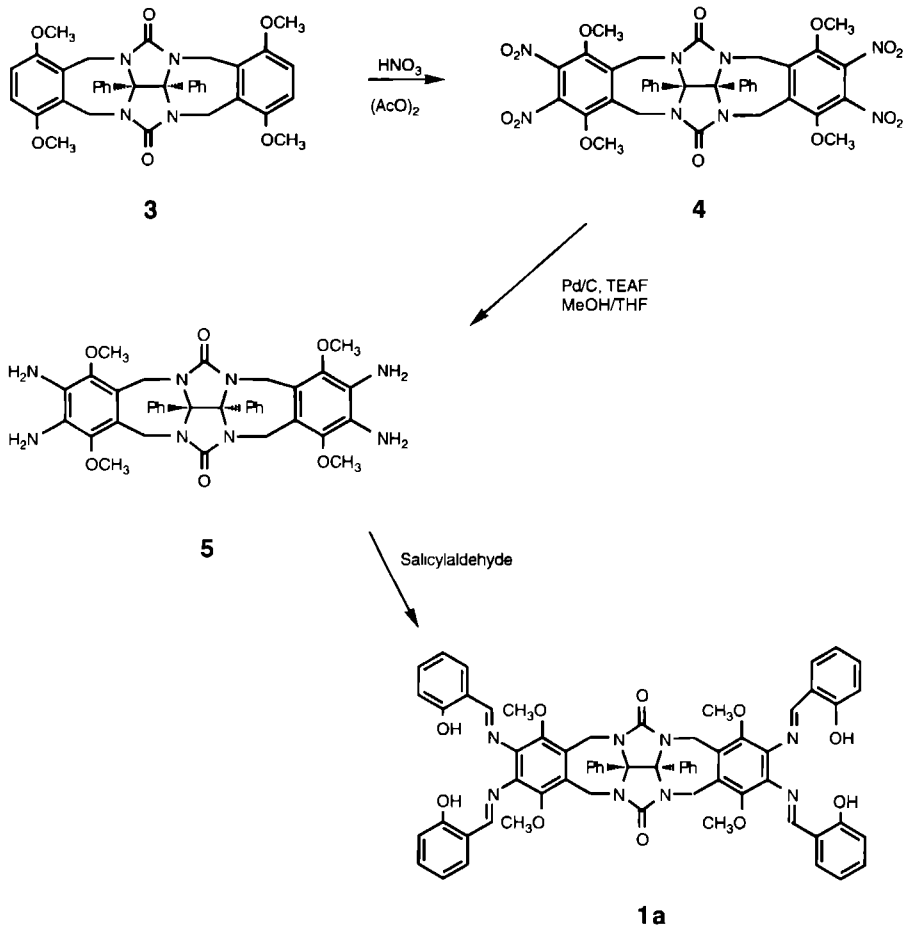
***Figure 8.1** Mode of binding of 1,3-dihydroxybenzene in molecular clip **3**. Binding occurs by hydrogen bonding and π-π stacking interactions.*

8.2 Results and discussion

8.2.1 Synthesis of binuclear nickel(II) and manganese(III) cavity-containing complexes 1b and 1c

The synthesis of the diphenylglycoluril clip **3** has been described elsewhere [12] Metal-free **1a** was prepared from **3** according to Scheme 8.1.

Scheme 8.1



3 **4** **5** **1a**

Treatment of **3** with an excess of fuming nitric acid in acetic anhydride gave the tetranitro-compound **4** in 85% yield. This compound was efficiently reduced to the tetraamine **5** in methanol/THF with triethylammonium formate and palladium on carbon as catalyst. Because compound **5** is sensitive to oxidation, it was not isolated from the reaction mixture. The latter mixture was filtered over Celite under a nitrogen atmosphere to remove the Pd/C catalyst, and after removal of the solvent, immediately treated with six equivalents of freshly distilled 2-hydroxybenzaldehyde (salicylaldehyde) in THF/methanol to when 3Å molecular sieves had been added Compound **1a** was isolated as a beige powder in 45% yield. The nickel(II) and manganese(III) metal complexes **1b** and **1c** were prepared by treating the ligand with 2.0 mol equivalents of the appropriate metal acetate salt in THF/methanol. Precipitation with additional methanol and filtration afforded the complexes as pure products. Alternatively, **1b** was prepared directly from **5** in the presence of salicylaldehyde and nickel(II) acetate tetrahydrate in

which case the nickel(II) ion acts as a template affording higher yields of the binuclear nickel(II) product.

8.2.2 X-ray diffraction structure of the cavity-containing binuclear nickel(II) complex 1b

Single crystals of the nickel(II) complex **1b** were grown in $CHCl_3$ by slow additon of methanol. The solid-state structure was determined by X-ray analysis Crystals of **1b** are triclinic, space group $P\bar{1}$, with a = 12.588(3), b = 16.855(4), c = 18.415(4) Å, α = 73.10(2), β = 76.96(2), γ = 75.89(2) Å. The result is shown in Figure 8.2. Examination of the X-ray structure of **1b** reveals that there is a twist in the cleft molecule. This twist at the base of the compound gives the complex an intrinsic chirality. An additional observation is that two of the methoxy groups on the cleft walls are pointing in the cavity, and the other two face outward.

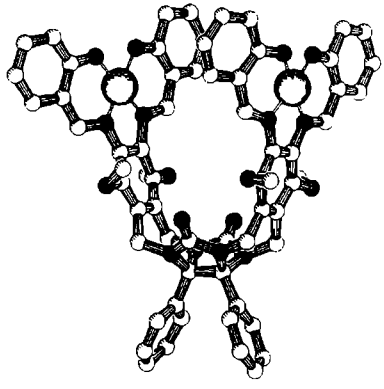


***Figure 8.2** X-ray structure of **1b**.*

A space filling representation of the X-ray structure (as drawn in Figure 8.3 B) shows that the carbonyl groups of the diphenyglycoluril moiety are blocked from hydrogen bonding Part of the binding site in the cavity is thus obstructed

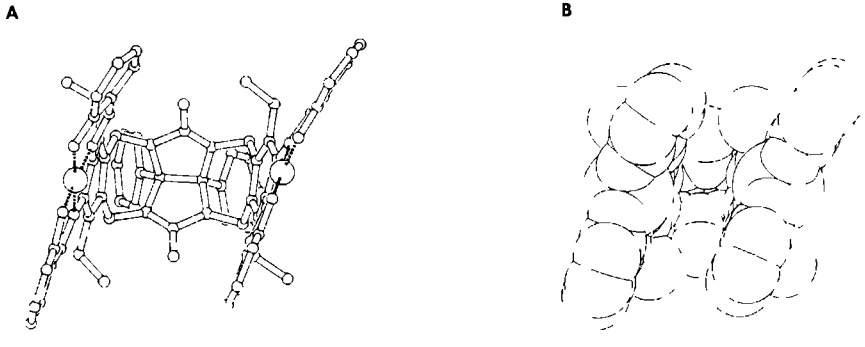


***Figure 8.3** Top view (A) and space-filling representation (B) of the X-ray structure of **1b**.*

8.2.3 Binding properties

Compound **3** binds a variety of dihydroxybenzenes in $CDCl_3$ solution.[8] Due to the square planar coordination around the Ni(II) ions, complex **1b** is diamagnetic and it was possible to investigate with ^{1}H-NMR the binding properties of **1b** using similar titration techniques as used in determining the binding constants of compound **3**.

When a solution of **1b** was titrated with resorcinol, the proton signals of **1b** shifted and broadened. The imine proton signals, in particular, became very broad. The signals of the resorcinol protons broadened as well. The OH-proton signal of resorcinol shifted downfield relative to its position in free resorcinol, whereas the aromatic proton signals did not shift. These observations can probably be explained if resorcinol forms a complex with **1b** that changes the coordination around the metal giving rise to a paramagnetic nickel species [17] Control experiments with resorcinol and nickel(II) salophen did not, however, show any broadening of the salophen ligand peaks as seen with ^{1}H-NMR. From these data, it appears that resorcinol most likely does not bind in the cavity of **1b**. This lack of binding can be partly explained by the twisted geometry of the host molecule which causes the cavity to be partially occluded, and by the fact that the carbonyl groups are blocked so that they cannot participate in hydrogen bonding (see previous section).

8.2.4 Epoxidation

In order to determine whether or not the functionalized nickel(II) and manganese(III) salen complexes were active as catalysts, a number of reactions were carried out with a variety of substrates using either NaOCl or iodosylbenzene as the terminal oxidant.[13-16] Some substrates such as styrene, allylbenzene, and *cis*- and *trans*-stilbene were chosen for their flat geometry and their ability to participate in π-stacking interactions with the walls of the cleft.[8] Other substrates such as α- and β-pinene were chosen for the bulkiness of their geometry, so that they would fit into the cleft less easily. Aromatic substrates with dihydroxy substituents were not used because these molecules are not preferably bound in the cavities of **1b** and, by analogy, **1c** as described in the previous section.

Results using the bis-nickel(II) clip **1b** with NaOCl as oxidant under two-phase reaction conditions are shown in Table 8.1

Table 8.1 Epoxidation results with **1b** and sodium hypochlorite[a]

Entry	Substrate	% Conversion	% Yield epoxide
1	Styrene	49	24
2	Cyclohexene	27	12
3	α-Pinene	23	10

[a]Reaction conditions 3.0 mmol alkene, 0.15 mmol benzyltributylammonium chloride (phase transfer catalyst), 2.0 mol % catalyst, 5.0 cm^3 dichloromethane, 5.0 cm^3 sodium hypochlorite solution (untitrated household bleach), T = 25 °C Reaction time = 3 h

Styrene was epoxidized in 24% yield, with a substrate conversion of 49%. Not only was the selectivity poor, but the catalyst degraded in a short time (approx 30 minutes) after the start of the reaction. The reaction mixture which was bright red at the beginning of the reaction due to the deep red of complex **1b**, slowly faded until it became colorless. We concluded that this bleaching of the solution was a result of the breakdown of the square planar nickel part of the complex. Complex **1b** was also able to epoxidize the electron-poor alkenes, cyclohexene and α-pinene, but in lower yields than styrene. It was also capable of epoxidizing α-pinene in the presence of O_2 and isobutyraldehyde, but it was not possible to establish whether the oxygen transfer occurred inside or outside the cleft, in the case of both types of oxidants. Therefore, further experiments were carried out using complex **1c** in the presence of 4-methylpyridine. This ligand acts as an axial ligand which, due to its large size can only coordinate to the manganese ion on the outside of the cleft. In this way it was possible to increase the likelihood that oxygen transfer to the substrate would occur inside the cavity of the catalyst These experiments could not be carried out with **1b** because the nickel center in the complex cannot expand its coordination sphere by binding an axial ligand. The results using complex **1c** as catalyst are shown in Table 8.2.

Table 8.2 Epoxidation results with complex **1c** as catalyst[a]

Substrate	% Conversion	% Yield epoxide
α-Pinene	47	20
β-Pinene	74	16
Cyclohexene	4	2
Styrene	39	34
Allylbenzene	6	4
trans-Stilbene	53	40
cis-Stilbene	33	26

[a]Reaction conditions 0 3 mmol alkene, 0 15 mmol iodosylbenzene, 3 0 mole % catalyst, 30 0 mmole 4-methylpyridine (axial ligand), and 5 0 cm^3 dichloromethane, 25 °C, N_2 atmosphere Reaction time = 3 h

To determine the ability of the cavity-containing cleft to discriminate between substrates based on their geometry and π-stacking ability, we also carried out a series of experiments with the non-functionalized manganese(III) salophen catalyst **2c**. The results are shown in Table 8.3

As can be seen from the data in Tables 8.2 and 8.3 there is little difference in yields between the two catalysts, except in the case of styrene which gave a yield with the cavity-containing catalyst more than twice that with the manganese(III)salophen catalyst. It is possible that π-π stacking interactions between complex **1c** and styrene contributed to the higher epoxide yields found with the cleft-containing catalyst.

Table 8.3 Epoxidation results with Mn(III)salophen **2c** as catalyst[a]

Substrate	% Conversion	% Yield epoxide
α-Pinene	34	15
β-Pinene	76	19
Cyclohexene	2	<1
Styrene	39	19
Allylbenzene	9	7
trans-Stilbene	49	36
cis-Stilbene	30	24

[a]Reaction conditions 0.3 mmol alkene, 0.15 mmol iodosylbenzene, 3.0 mol % catalyst, 3.0 mmol (50.0 mole equivalents) 4-methylpyridine (axial ligand), and 5.0 cm^3 dichloromethane, 25 °C, N_2 atmosphere. Reaction time = 3 h.

8.2.5 Investigations with dihydroxybenzene as additive in epoxidation reactions catalyzed by manganese(III) and nickel(II) salophen complexes

All of the substrates mentioned thus far in epoxidation reactions using either NaOCl or iodosylbenzene as oxygen atom donor were non-functionalized alkenes. It was not necessary to be concerned about the reactivity of additional functional groups attached to the substrate. The molecular clips described in this chapter were designed, however, to bind a substrate *via* hydrogen bonds and π-stacking interactions. This type of binding necessitates that the substrates have a particular shape and are modified with groups that can participate in hydrogen bonding with the carbonyl groups of the molecular clip. Previous research in our laboratory had shown that dihydroxybenzenes are extremely suited for binding in the cleft *via* π-π stacking interactions and hydrogen bonding.[8] In order to determine whether or not the hydroxyl groups have an effect on the epoxidation of the double bond in 1-allyl-3,5-dihydroxybenzene we investigated the epoxidation of this molecule using ni(ckelII) salophen and manganese(III) salophen as test catalysts. Preliminary results revealed that, in contrast to allylbenzene, 3,5-dihydroxy allylbenzene was not epoxidized by manganese(III) salophen and iodosylbenzene. The difference between these two substrates is of course the aryl-hydroxy groups that are necessary for binding in complex **1b**. To further investigate the effect that aryl hydroxy groups have on the epoxidation reaction, a number of experiments using styrene and α-pinene as substrates in the presence of resorcinol were carried out. The results with manganese(III) salophen as catalyst and iodosylbenzene as oxidant are shown in Table 8.4.

Table 8.4 Results of epoxidation reactions with Mn(III)salophen as catalyst and iodosylbenzene as oxygen atom donor[a]

Entry	Substrate	Additive[b]	% Yield epoxide[c]	Turnover #[d]
1	Styrene	–	38	6
2	Styrene[e]	–	54	8
3	Styrene	Resorcinol (2 0 mol equiv)	0	0
4	Styrene	Resorcinol (0 07 mol equiv)	38	6
5	Styrene	Ethanol (3 0 mol equiv)	45	7
6	Styrene	*t*-Butanol (3 0 mol equiv)	48	7
7	Styrene	4 *t* Bu 2-Me-phenol (0 07 mol equiv)	39	6
8	α Pinene	–	62	9
9	α Pinene	Resorcinol (2 0 mol equiv)	0	0
10	Styrene[f]	3,5 Dihydroxystyrene (2 0 mol equiv)	4	<1
11	Styrene	3 5 Dihydroxystyrene (0 1 mol equiv)	40	6
12	3 5 Dimethoxystyrene	–	32[g]	3

a Reaction conditions 0 01 mmol Mn(III)salophen 0 3 mmol substrate, 0 5 mmol 4 picoline and 0 15 mmol iodosylbenzene in 5 0 ml dichloromethane Reaction time = 3h
b Mole equivalents respective to the concentration of iodosylbenzene
c Epoxide yield = mmol epoxide / mmol iodosylbenzene x 100%
d Turnover # = mmol epoxide / mmol catalyst x 100%
e 0 1 Mmol styrene and 0 05 mmol iodosylbenzene
f Reaction carried out without 4 picoline
g 7 % 3 5 Dimethoxy-2-phenylacetaldehyde is also formed as determined by GC MS

In the absence of resorcinol (entry 1) styrene is converted to its epoxide in 38% yield after three hours reaction time In the absence of 4-picoline, an axial ligand, styrene is epoxidized in 54% yield The addition of 4-picoline in this case, may block access of the iodosylbenzene molecule to the maanganese(III) center 4-Picoline was used in the reactions with the cavity containing catalyst **1c** to prevent oxygen transfer from occurring on the outside of the cavity In the same reaction (entry 3) in the presence of 2 0 mole equivalents resorcinol, no epoxide is formed The influence of the amount of resorcinol on the yield of epoxide was determined by carrying out several reactions in the presence of various amounts of resorcinol The results are shown in Figure 8 4

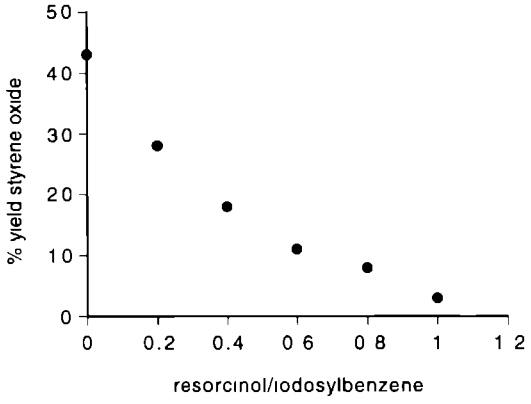


Figure 8.4 *Effect of resorcinol on the yield of styrene epoxide*

The results shown in this figure clearly show the inhibiting effect of resorcinol on the formation of epoxide from styrene. At a 1:1 ratio of resorcinol to iodosylbenzene, only a trace amount of styrene epoxide is formed. To determine whether or not this inhibition effect was a result of poisoning of the catalyst or that of a competing side reaction, we decided to investigate the fate of resorcinol under standard reaction conditions with iodosylbenzene in the absence of alkene, and in the absence and presence of manganese(III) salophen. In the absence of manganese(III)salophen only 6% resorcinol remained unconverted after 1 hour reaction time. If manganese(III) salophen was included in the reaction mixture, no resorcinol remained after 20 minutes reaction time. The addition of aliphatic alcohols such as ethanol or *t*-butanol, however, had the effect of actually increasing the yield of epoxide (Table 8 4, entries 5 and 6). Furthermore the yield of epoxide appeared not to be affected by the addition of a standard radical trapping compound such as 4-*t*-butyl-2-methylphenol,[19] so that the inhibition of resorcinol on the reaction does not appear to come from its radical trapping behavior Resorcinol also reduced the amount of epoxide formed when α-pinene was used as a substrate, in the same manner as it did with styrene. In the absence of resorcinol, 62% α-pinene epoxide was found. In the presence of 2.0 mole equivalents of resorcinol, no α-pinene epoxide was formed The addition of 3,5-dihydroxystyrene (entries 10 and 11) gave the same negative result: only 3,5-dihydroxystyrene was converted to non-epoxide oxidation products The oxidation of 3,5-dimethoxystyrene with iodosylbenzene and manganese(III) salophen resulted in a yield of 32% of the corresponding epoxide and 7% 3,5-dimethoxy-2-phenyl acetaldehyde.

The results listed in Table 8.4 suggest that the hydroxy groups of resorcinol and 3,5-dihydroxystyrene are oxidized by iodosylbenzene in the presence and absence of manganese(III)salophen as transition metal catalyst. The exact nature of the oxidation products formed was not investigated The arylhydroxy groups are likely oxidized to peroxy groups. The faster conversion of resorcinol in the presence of manganese(III)salophen suggests that the presumed Mn(V)-oxo-complex that is formed from manganese(III) and iodosylbenzene[20] is also able to oxidize the hydroxy groups of the resorcinol molecule.

In a second series of experiments we investigated the epoxidation of aryl alkenes modified with hydroxyl groups by molecular oxygen, catalyzed by nickel(II) salophen in the presence of oxygen and isobutyraldehyde.[21,22] The results of these investigations are shown in Table 8.5.

Table 8.5 Epoxidation of alkenes with nickel(II) salophen as catalyst and molecular oxygen as oxygen atom donor in conjunction with isobutryaldehyde under various conditions[a]

Entry	Substrate	Additive[b]	% Yield epoxide[c]	Turnover #[d]
1	Styrene	–	26	6
2	Styrene	Resorcinol (1 0 mol equiv)	0	0
3	Styrene	Resorcinol (0 1 mol equiv)	0[e]	0
4	Styrene	Resorcinol (0 004 mol equiv)	0[e]	0
5	Styrene	*t*-Butanol (1 0 mol equiv)	10	5
6	Styrene	Ethanol (1 0 mol equiv)	10	5
7	α-Pinene	–	71	35
8	α-Pinene	Resorcinol (0.25 mol equiv)	0	0
9	Styrene	2-*t*-Bu-4-Me-phenol (0 017 mol equiv)	1	<1
10	Styrene[f]	3,5-Dihydroxystyrene (1 0 mol equiv)	0	0
11	Styrene[g]	3,5-Dihydroxystyrene (0 1 mol equiv)	0	0

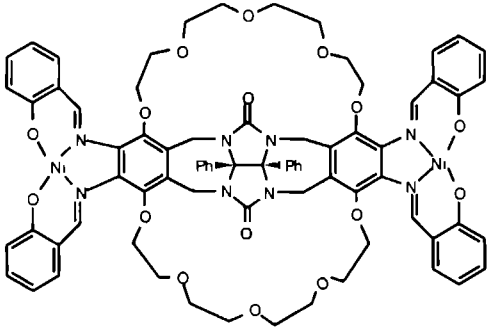
a Reaction conditions 0 012 mmol Ni(II)salophen, 0 6 mmol substrate, 1 8 mmol isobutyraldehyde, 1 0 atmosphere O_2, in 5 0 cm^3 dichloromethane Epoxide yield was determined after 3 hrs reaction time at room temperature
b Mole equivalents respective to the amount of substrate
c Epoxide yield = mmol epoxide / mmol substrate x 100%
d Turnover # = mmol epoxide / mmole catalyst x 100%
e A trace of epoxide is formed, but in all cases less than 0 2 %
f 0 1 Mmol styrene and 0 3 mmol isobutyraldehyde was used
g 0 3 Mmol styrene and 0 9 mmol isobutyraldehyde was used

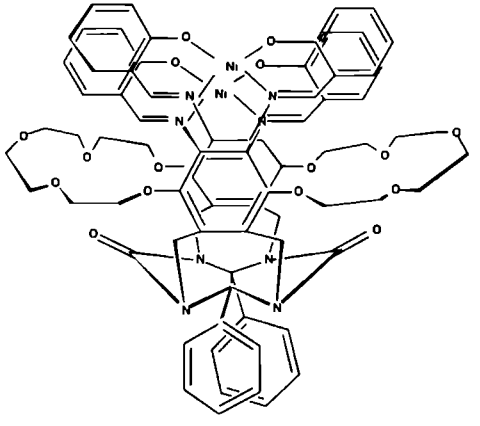
In the presence of nickel(II)salophen, O_2, and isobutyraldehyde, styrene was converted to its epoxide in 26% yield (entry 1). When 0.004 - 1.0 mole equivalent of resorcinol was added to the reaction mixture, no conversion of styrene occurred (entries 2-4). Even small amounts of resorcinol (entry 4) added to the reaction mixture inhibited the reaction completely. The addition of aliphatic alcohols such as ethanol and *tert*-butanol (entries 5 and 6) had the effect of inhibiting the reaction, but not completely blocking it. These results are consistent with those found using nickel(II) β-diketonate complexes as catalysts as described in Chapter 6. Resorcinol acts as a radical trapping compound which is able to completely inhibit the

reaction,[19] while aliphatic alcohols compete with isobutyraldehyde for the vacant coordination sites on the nickel catalyst, thereby slowing the turnover rate.

8.2.6 A binuclear nickel(II) cavity-containing complex modified with crown-ether bridges

A second cavity-containing molecule, one modified with crown ether bridges (**6**), was designed to avoid the problem of blocking the cavity with groups that could rotate into the cleft. Futhermore, the crown ether groups attached to the walls of the cleft provide an additional mode of binding to the molecule. For example, quarternary amines functionalized with a double bond could also bind in the crown ether portion of the complex.[18]





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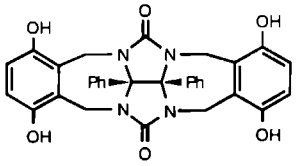
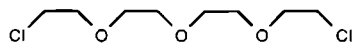
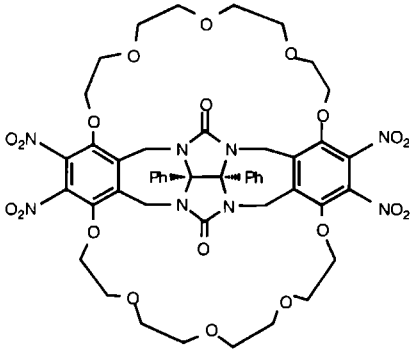


7

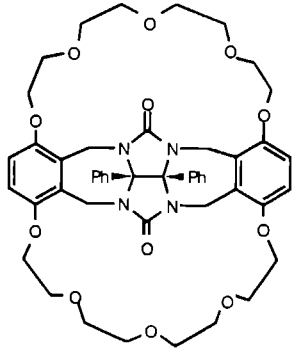




9

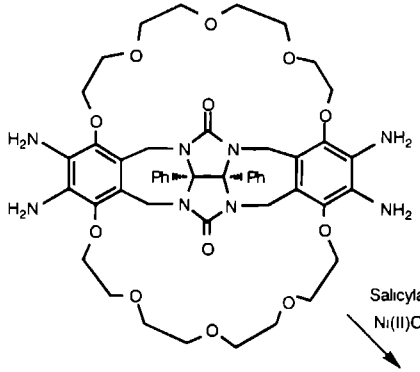
HNO_3

$(AcO)_2$



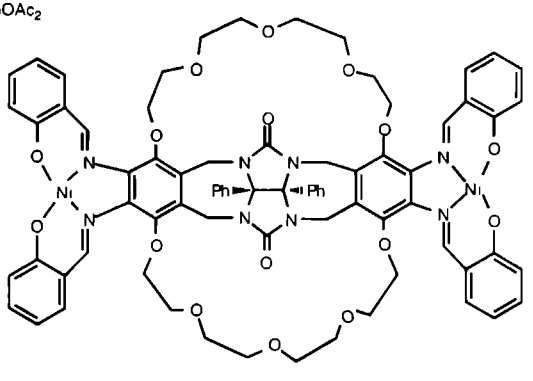
8

Pd/C
TEAF
THF/methanol



10

Salicylaldehyde
$Ni(II)OAc_2$



6

Scheme 8 2

8.2.7 Synthesis of complex 6

Compound **6** was prepared according to Scheme 8 2 The synthesis of the tetrahydroxy clip **7** has been reported elsewhere [12] Compound **7** was reacted with 2 0 mol equivalents of the dichloro ether compound to give **8** in 64% yield The crown ether clip **8** was nitrated with concentrated HNO_3 in acetic anyhydride to give the tetranitro crown ether complex **9** (87% yield) The tetranitro crown ether clip, **9**, was subsequently reduced to the corresponding tetraamino compound **10** with Pd/C and triethylammonium formate The air-sensitive compound **10** was immediately reacted with 6 0 mol equivalents of freshly distilled salicylaldehyde and 2 0 mol equivalents of nickel(II) acetate tetrahydrate in THF/methanol to give a mixture of **6** and a compound where one side of the cleft is modified with the nickel salophen group and the other side of the cleft remains unmodified, but with oxidized amino groups The exact structure of the latter compound was not determined

8.2.8 Binding studies of crown ether complex 8

Although we were unable to obtain complex **6** in pure form for binding studies, we were able to determine the binding capabilities of the crown ether clip, **8** with resorcinol Upon addition of one mole equivalent resorcinol to a $CDCl_3$ solution of crown ether clip **8** the peak positions of both the clip protons and the resorcinol protons were shifted The binding affinity of resorcinol was determined by a ^{1}H-NMR titration experiment $CDCl_3$ The average binding constant that was determined from several titrations was $K_a = (1\ 7 \pm 0\ 3) \times 10^3$ dm^3 mol^{-1} (Table 8 6)

Table 8.6 K_a and CIS-values for the titration of **6** with resorcinol

Experiment	K_a (dm^3 mol^{-1})x 10^3	CIS (ppm)
1	1 77	-2 28
2	1 68	-0 45
3	1 78	-0 36
	average $K_a = (1\ 7 \pm 0\ 3) \times 10^3$	

8.2.9 X-ray structure of the tetranitro crown ether clip 9

We were able to grow single crystals of **9** which were suitable for X ray diffraction by slow evaporation of a chloroform solution of this compound [23] Side and bottom views of the solved structure are shown in Figure 8 5 It is easily seen from these structures that the crown ether portion of the compound is open i e occlusion of the cleft opening does not occur Whether or not this open structure is maintained in solution is not known, but based on the solved structure it is possible to presume that an open crown ether ring conformation can be adopted in solution by complex **6**

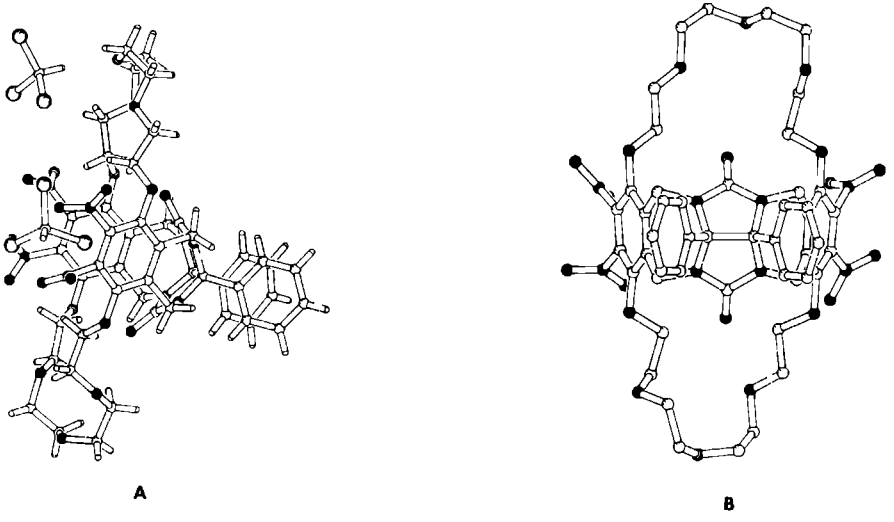


Figure 8.5 X-ray structure of 9 Side (A) and top (B) views

8.2.10 Epoxidation

Several attempts were made to separate complex **6** from the reaction products that were contaminated with a compound that had undergone only partial condensation with salicylaldehyde None of these separation attempts including re-crystallization, and column chromatography with silica gel, alumina, or sephadex were successful It was not possible, therefore to carry out epoxidation reactions with pure material

8.3 Concluding remarks

We have shown that it is possible to modify a molecular clip with a transition metal-containing salen moiety to give an active epoxidation catalyst We were not, however, able to observe selective epoxidation with metallo-clip **1b** and **1c** due to the fact that the cleft is partially occluded by the methoxy groups attached to the walls of the cleft, that turn inward into the cavity The crown ether metallo-clip, **6**, afforded a solution to the problem of blockage of the cavity by modifying the walls of the clip with crown ether groups that remained open and outside of the cavity so as not to interfere with the binding of potential substrates Even though binding of dihydroxybenzenes will probably occur with metallo-clip **6**, epoxidation of a double bond on a substituted dihydroxy benzene would most likely not proceed due to either oxidation of the aryl hydroxy groups or inhibition of the reaction by acting as a radical trapping compound in the case where aldehyde/O_2 is used as the oxidant The addition of the crown ether groups to the molecular clip does allow for other substrates, such as those with quaternary

ammonium groups to bind inside the cavity due to the interaction between the crown ether oxygen and the quaternary ammonium. In this way it might be possible to achieve selective epoxidation of an appropriately modified alkene

8.4 Experimental

Materials. 2-Hydroxybenzoic acid (salicylaldehyde) and o-phenylenediamine were purchased from Aldrich Salicylaldehyde was distilled immediately prior to use. 3,5-Dimethoxybenzaldehyde was also purched from Aldrich. All other reagents, unless otherwise indicated were used as received. Tetrahydrofuran was distilled over sodium metal/benzophenone and stored over 4Å molecular sieves. Methanol was HPLC grade and stored over 3Å molecular sieves.

Instrumentation. ^{1}H-NMR spectra were taken on a Bruker AC 100 MHz-spectrometer Chemical shifts (δ) are given in ppm downfield from TMS IR spectra were taken on a Perkin Elmer 1720-X Infra-red Fourier Transform spectrometer. GC-analyses were carried out on a Varian 3700 gas chromatograph with a flame ionization detector, coupled to a Hewlett Packard 3395 integrator, column: CP-sil, 25 m, 25 μm diam., Temp. Prog. 80 °C, 2 min., 10 °C/min., 250 °C, 2 min.) HPLC-analyses were carried out on a LKB Bromma 2150 HPLC ramp and 2152 HPLC controller, coupled to a LKB Bromma 2221 integrator. UV-visible spectra were taken on a Perkin Elmer Lambda 5 spectrometer. Elemental analyses were determined with a Carlo Erba Ea 1108. Mass spectra were taken on a VG 7060 E spectrometer. Melting points are uncorrected

Syntheses.

5,7,12,13b,13c,14-hexahydro-1,4,8,11-tetramethoxy-2,3,9,10-tetranitro-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[f]azulene-6,13-dione (4). An ice cold solution of 8.75 cm^3 aqueous 65% HNO_3 and 35 0 cm^3 acetic anhydride was added to a stirring solution of 5 0 grams of molecular clip **3** in 40 0 cm^3 acetic anhydride at -70 °C After addition of the HNO_3 solution the reaction was allowed to warm to room temperature. The reaction mixture was stirred for several hours or overnight 75 0 cm^3 of cold methanol was added to the reaction flask and a pale yellow precipitate was filtered from the reaction mixture and washed with cold methanol. Yield 87% of a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ· 7.15 (m, 10 H, ArH), 5.56 and 3 90 (2d, 8 H, NC*H*HAr, J = 15 8 Hz), 4.10 (s, 12 H OMe); IR (KBR) ν_{max} cm^{-1}: 1715, 1565, 1540, 1355 cm ^{1}; FAB-MS (*m*-nitrobenzylalcohol) m/z 799 (M+H)$^+$. Anal. Calcd for $C_{36}H_{30}N_8O_{14}$ CH_3COOH: C, 53.15, H, 3.99; N, 13.05. Found: C, 53.13; H, 3.83; N, 12.99.

5,7,12,13b,13c,14-hexahydro-1,4,8,11-tetramethoxy-2,3,9,10-tetramino-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[f]azulene-6,13-dione (5). A solution of 1.0 g of the tetranitro clip, **4**, in THF/Methanol (100 cm^3, 3:1, v/v) was degassed by bubbling nitrogen through it for 20 min The solution was stirred under an atmosphere of nitrogen and to this stirring solution was added 300 mg Pd/C (10% palladium) and 4.0 cm^3 triethylammonium formate. The solution was stirred over 3Å molecular sieves for 4 hrs after which stirring was stopped and the reaction mixture filtered using Schlenk apparatus to remove the Pd/C and molecular sieves. After removal of solvent, the tetranitro amino clip (which is extremely air-sensitive) was used

directly in the next reaction step without further work up. Yield: 100%, of a pale yellow oil ^{1}H-NMR ($CDCl_3$) δ: 7 08 (m, 10 H, ArH), 5.38 and 3.80 (2d, 8 H, NC*H*HAr, J = 15 8 Hz), 4 74 (br s, 8 H, NH_2), 3.80 (s, 12 H, OMe); FAB-MS (*m*-nitrobenzylalcohol) m/z 679 $(M+H)^+$.

Compound 1a. Tetraamino clip, **5** (1.0 g) was dissolved in a degassed solution of THF/methanol (100 cm^3, 2:1, v/v). 3Å molecular sieves were added to the reaction flask and the mixture was stirred at room temperature under an atmosphere of nitrogen. To the stirring reaction mixture was added dropwise 6.0 mol equiv. of freshly distilled salicylaldehyde which had been diluted in 50.0 cm^3 of THF/methanol, 2:1, v/v. The solution was allowed to stir at room temperature under a nitrogen atmosphere for several hrs or overnight after which the reaction was filtered over Celite to remove the molecular sieves. The solvent was removed from the filtrate and the product was precipitated by the addition of methanol Yield· 45% of a beige powder ^{1}H-NMR ($CDCl_3$) δ· 8.45, (s, 4H, imine CH); 7.09, (s, 10H, ArH); 6.94-6.70, (m, 12H, saloph ArH); 5.70 and 3.89, (2d, 8H, NCH Ar, J = 15.8 Hz); 3.62, (s, 12H, OMe); IR (KBR) (ν_{max} cm^{-1}): 1711 (C=O), 1618 (C=N), 1460 (C-O). M.p. > 400 °C

[μ-[5,7,12,13b,13c,14-hexahydro-2,3,9,10-tetrakis[[(2-hydroxyphenyl) methylene]amino]-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[f]azulene-6,13-dionato(4-)-N^2,N^3,O^2,O^3:N^9,N^{10},O^9,O^{10}]] dinickel (1b). To stirring solution of 300 mg of the free ligand, **1a**, in THF/methanol (30.0 cm^3, 2·1, v/v) was added 2.0 mol equiv Ni(II) acetate tetrahydrate that had been dissolved in 5.0 cm^3 methanol. The pale brown solution of the free ligand turned immediately a dark red upon addition of the nickel salt indicating that complexation of the nickel ion had occurred. The solution was stirred for 30 min. and the product was precipitated by the addition of cold methanol. The dark red crystalline material was filtered from the reaction mixture and washed with several portions of cold methanol and finally with ether Yield: 83% of dark red crystals. ^{1}H-NMR ($CDCl_3$) δ· 8.98, (s, 4H, imine CH), 7.2, (s, 10H, ArH), 7.14-6.98, (m, 2d, 8H, NCH Ar, J = 15.8 Hz), 3 67, (s, 12H, OMe) IR (KBr) ν_{max} cm^{-1}· 1712 (C=O), 1608 (C=N), 1523, 1448. FAB-MS (3-nitrobenzyl alcohol) *m/z:* 1207 $(M+H)^+$ Anal calcd for $C_{64}H_{50}N_8O_{10}Ni_2$ $CHCl_3$ MeOH: C 58.29, H 4 08, N 8.24, found. C 58.89, H 4.21, N 8 22

[μ-[5,7,12,13b,13c,14-hexahydro-2,3,9,10-tetrakis[[(2-hydroxyphenyl) methylene]amino]-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[f]azulene-6,13-dionato(4-)-N^2,N^3,O^2,O^3:N^9,N^{10},O^9,O^{10}]] dimanganese (1c). To a stirring solution of 300 mg of the free ligand, **1a**, in a solution of THF/methanol (30.0 cm^3, 2.1, v/v) was added 2.0 mole equivalents Mn(II) acetate tetrahydrate that had been dissolved in 5.0 cm^3 methanol. The resulting pale brown solution was stirred vigorously in air and after several min , became very dark brown indicating complexation of the Mn(II) ion into the ligand and subsequent oxidation to Mn(III). The solvent was removed from the flask and the product was precipitated by the addition of ether. The precipitate was filtered and washed with several portions of ice cold methanol and water and then dried in air. Yield: 75% of dark brown crystals. IR (KBR) ν_{max} cm^{-1}: 1713 (C=O), 1603 (C=N), 1586, 1530 FAB-MS (3-nitrobenzyl alcohol) *m/z.* 1198 $(M-2CH_3COO)^+$, Anal. calcd for $C_{68}N_8O_{14}H_{56}Mn_2$ $2H_2O$ C 60 27, H 4.46, N 8.27; found: C 60.30, H 4.48, N, 8.16.

Tetranitro crown ether clip, 9. To an ice-cold suspension of crown-ether clip, **8** (6 00 g, 7 02 mmol) in 55 0 cm^3 acetic anhydride was added 7 7 cm^3 aqueous 65% nitric acid that had been diluted with 55 0 cm^3 acetic anhydride After allowing the reaction mixture to warm to room temperature, it was stirred for 20 hrs at 25 °C The reaction was stopped and 180 cm^3 methanol was added to the reaction flask The solvent was removed and the residue was dissolved in 30 0 cm^3 chloroform Addition of 100 cm^3 methanol caused a precipitate to form The solid material was filtered and washed with aqueous 1N NaOH and several portions of water and dried Yield 60 % (4 2 g) of a pale yellow powder ^{1}H-NMR ($CDCl_3$) δ 7 16 (s, 10H, ArH), 5 59 (d, 4H, N-C*H*H-Ar), 4 73 (m, 4H, ArO-C*H*H-), 4 4 3 6 (m, 32H, ArO CH*H*-, N CH*H*-Ar, other CH_2-protons) FAB MS (3 nitrobenzyl alcohol) *m/z* 1059 $(M+H)^+$ and 1081 $(M+Na)^+$ Anal Calcd for $C_{48}H_{50}N_8O_{20}$ C 54 44, H 4 76, N 10 58, found C 54 47, H 4 77, N 10 54

Tetraamino crown ether clip, 10. To a suspension of tetranitro clip, **9** (0 380 g, 0 37 mmol) in 25 0 cm^3 degassed dry THF/methanol (2 1 v/v) was added 200 mg palladium on activated charcoal (Pd/C, 10%) and 2 5 cm^3 triethylammonium formate (TEAF) The reaction mixture was stirred under an atmosphere of nitrogen until the formation of CO_2 ceased (approx 2 days) The reaction mixture was filtered in a glass filter over Celite using Schlenk techniques to exclude oxygen from the reaction flask The product was used further without additional workup

Compound 6. This compound was prepared by reacting compound 10 with six equivalents of salicyladehyde in a manner similar to that described for compound **1a**, except that Ni(II)OAc_2 was also added to the reaction mixture to act as a template ion and to facilitate the Schiff base reaction As described in the text, we were not able to obtain pure material of this compound The analyzed (FAB-MS) product mixture showed there to be about 10% of compound **6** which we were not able to isolate

Salophen, 2a. The salophen ligand was prepared by adding 2 0 mole equivalents of 2 hydroxy benzaldehyde (salicylaldehyde) to a stirring solution of *o*-phenylenediamine in methanol under a nitrogen atmosphere in the presence of 3 Å molecular sieves After stirring for several minutes the bright yellow product began to precipitate from the solution After stirring for an additional 30 minutes, the reaction was stopped The reaction mixture was concentrated by vacuum removal of the solvent and the product was filtered and washed with ice-cold methanol Yield 86% ^{1}H NMR ($CDCl_3$) δ 13 08 (s, 2H, OH), 8 59 (s, 2H HC=N), 7 44-6 80 (m, 12H, ArH) IR (KBr) ν_{max} cm^{-1} 1612 (C=N), 1562, 1481 M p = 390-391 °C

[Mn(III) salophen]Cl, 2c. To prepare the Mn(III) salophen complex, 0 5 mmoles (157 mg) salophen was dissolved in 30 0 cm^3 of THF/methanol (2 1, v/v) The solution was refluxed under air at room temperature and to it was added dropwise a solution of 0 5 mmoles Mn(II) acetate tetrahydrate (124 mg) that had been dissolved in methanol (2 0 cm^3) The resulting solution turned dark brown After refluxing for 30 minutes an excess of LiCl was added to the solution and stirred for an addition 30 min The reaction mixture was cooled and allowed to stir at room temperature for 1 hour Air was bubbled through the solution for 20 minutes during which time a dark solid precipitated from the solution The reaction mixture was concentrated and the product was filtered and washed with several portions of ice cold water, then with petroleum ether and dried in air to give a dark brown crystalline material Yield 79% IR (KBr) ν_{max} cm^{-1} 1605 (C=N), 1377 (C-H, imine), 1286 (C-O) M p > 400 °C

Nickel(II) salophen, 2b. 0.5 mmoles (157 mg) salophen was dissolved in 30.0 cm^3 of THF/methanol (2:1, v/v). The solution was stirred under air at room temperature and to this was added dropwise a solution of 0.5 mmoles Ni(II) acetate tetrahydrate (124 mg) that had been dissolved in methanol (2.0 cm^3). The resulting solution turned immediately dark red and the reaction was allowed to stir for 1 hour. The reaction was stopped and the solvent concentrated under vacuum. The product was precipitated by the addition of methanol and was filtered, washed with water, then cold methanol and dried in air to give a dark red crystalline material in 93% yield. IR (KBr) ν_{max} cm^{-1}: 1605 (C=N), 1577, 1522
M p. > 400 °C.

3,5-Dimethoxystyrene. A solution of potassium *t*-butanolate (8.29 g, 74.0 mmol) in 55.0 cm^3 dry dimethylsulfoxide was added dropwise to triphenylmethylphosphonium iodide (28 6 g, 70.9 mmol) under an atmosphere of nitrogen. After the salt was dissolved a solution of 3,5-dimethoxybenzaldehyde (4.0 g; 24 3 mml) in 5.0 cm^3 dry dimethylsulfoxide was added dropwise, causing the color of the reaction mixture to change from yellow to red After 20 hrs stirring at room temperature, the reaction mixture was poured onto ice to which a saturated aqueous NaCl solution had been added. The mixture was extracted with ether (3x), the organic layer was dried with magnesium sulfate and concentrated. After column chromatography ($CHCl_3$:MeOH, 98:2 v/v, silicagel) 3.20 g (81% yield) of a yellow oil was obtained. ^{1}H-NMR ($CDCl_3$) δ 6 57 (d x d, 1H, AR-CH-C=, J_{cis}=11 Hz, J_{trans}=17 Hz), 6.56 (d, 2H, ArH), 6 38 (t, 1H, ArH), 5.71 (d x d, 1H, C=CHH trans with respect to phenyl) 5 22 (d x d, 1 H, C=CHH cis with respect to phenyl), 3.77 (s, 6H, MeO-).

3,5-dihydroxystyrene. A suspension of 1.40 g (51.5 mmol) aluminum foil bits (washed with hexane and dichloromethane and dried) and 3.10 g (12.2 mmol) iodine in 80.0 cm^3 dry and O_2-free CS_2 was refluxed for 2 hrs under an atmosphere of nitrogen. To this solution was added 1.70 g (10.3 mmol) 3,5 dimethoxystyrene The reaction was followed by TLC (silica;ethylacetate/hexane 1/1, v/v). After the disappearance of the substrate as shown by TLC (approximately 24 hrs reaction time), 125 cm^3 of distilled water was added to the reaction mixture which was then extracted twice with diethylether. The ether layer was washed with sodium dithionite solution (2x) and distilled water (2x), dried with magnesium sulfate and concentrated to a light tan oil. After purification by column chromatography (ethyl acetate·hexane, 1:1 v/v, silicagel) the product was isolated as a light tan oil Crystallization to give an orange colored powder was possible in $CHCl_3$. Yield (after column chromatography). 0 70 g (50%) ^{1}H-NMR ($CDCl_3$) δ 6.58 (dd, 1H, Ar-CH=C-, J_{cis}=11 Hz, J_{trans} = 18 Hz), 6.47 (s, 2H, ArH), 6 26 (t, 1H, ArH), 5 69 (d, 1H, C=CH*H* cis with respect to phenyl) 5 24 (d, 1H, C=CH H trans with respect to phenyl), 4.74 (s, 2H, -OH).

Epoxidation reactions.
Epoxidation reactions using complexes **1b** and **1c** with NaOCl or iodosylbenzene as oxygen atom donors, respectively, were carried out as follows.

To a Schlenk tube (3 cm x 15 cm) was added 5.0 cm^3 dichloromethane, 3.0 mmol alkene, 0 10 mmol phase transfer catalyst (benzyltributylammonium chloride), 2.0 mol% catalyst (compound **1b**) and 5 0 cm^3 of sodium hypochlorite solution (untitrated household bleach) The reaction was stirred vigorously under a nitrogen atmosphere for 3 hours After the predetermined reaction time was over, the stirrer was stopped and and aliquot of the organic layer was removed. To this was added an internal standard (*o*-dichlorobenzene) and the sample was analyzed by gas chromatography.

To a Schlenk tube (3 cm x 15 cm) was added 5.0 cm^3 dichloromethane, 3.0 mmol alkene, 0 15 mmol iodosylbenzene, and 2.0 mol % catalyst (compound **1c** or Mn(III) salophen). The

reaction mixture was stirred vigorously under a nitrogen atmosphere for 3 hrs, at which time the stirred was stopped, an internal standard was added to the reaction and a sample was analyzed by gas chromatography (Column CP-sil, 25 m, 25 μm, diam , Temp program 80 °C, 2 min , 10 °C/min , 250 °C, 2 min)

Epoxidation of alkenes with molecular oxygen in the presence of isobutyraldehyde

A Schlenck tube (10 cm x 2 cm) was charged with 5 0 cm^3 dichloromethane, 80 μm^3 (0 5 mmol) α-pinene, 136 μm^3 (1 5 mmol) isobutyraldehyde and 1 0 mol % (respective to the alkene) catalyst The Schlenk tube was evacuated and then filled with O_2 The reaction mixture was stirred at 1000 rpm at 25 °C under 1 0 atomsphere O_2 for 6 hours at which time the reaction was stopped, an internal standard was added (*o* dichlorobenzene) and the mixture analyzed by GLC The stability of the catalysts was determined by measuring an aliquot from the reaction mixture at varying intervals by UV-vis spectroscopy

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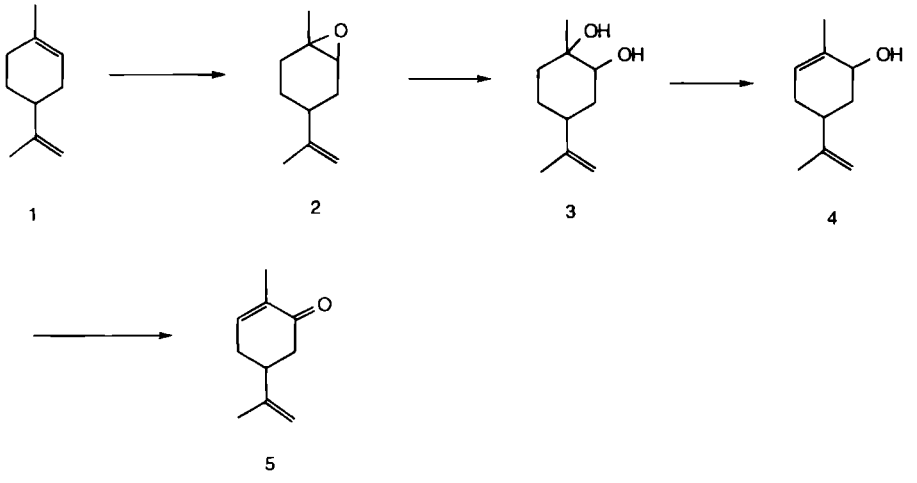
Epilogue

The work described in this thesis was carried out within the aims of the Innovative Oriented Research Program on Catalysis (IOP-Catalysis) of the Ministry of Economic Affairs The IOP-Catalysis program was established to promote the cooperation of universities and industry for the development of catalysts and catalyst systems that would be of interest for industrial scale applications The goal of the research described in this thesis was the development of catalyst systems for the epoxidation of alkenes by molecular oxygen In recent years, new technologies have been sought which allow for cheaper, more efficient, and milder oxidation processes that produce minimal waste products The use of molecular oxygen in place of more traditional oxidants in industrial processes is an important goal for the eventual improvement of current epoxidation processes Molecular oxygen poses some difficulties, however, in its use as an oxidant, the most important being the need for a sacrificial source of electrons for the reductive activation of this molecule Many laboratory investigations have looked to natural systems as a source of inspiration for developing synthetic means of catalyzing some of the same reactions as do enzymes with, of course, molecular oxygen as the oxidant

In that tradition we investigated the feasibility of using a manganese(III) porphyrin / rhodium(III) bipyridyl / formate catalyst system, using uncoupled complexes in a two-phase system and π-conjugated complexes to promote faster electron transfer between the manganese(III) porphyrin catalyst and the electron source Although this system is potentially of great scientific interest due to the insights it can give on electron transport and oxygen binding and activation, it is not practical for carrying out efficient epoxidation on a larger scale Epoxide yields were too low to be of synthetic utility and would need to be improved for this system to be used as a viable industrial process

We therefore explored the possibilites of a different catalyst system, involving the use of nickel(II) β-diketonate and nickel(II) oxamide ligands in conjunction with molecular oxygen and an aldehyde This system offers great promise for industrial scale preparations The catalysts are inexpensive and simple to prepare They are stable under the reaction conditions as long as there is sufficient reactive substrate in the reaction mixture Electron-poor alkenes, such as α-pinene, norbornene, cyclohexene, and limone, which are typically more difficult to epoxidize than electron-rich alkenes are particularly reactive and gave good to excellent yields with high selectivity (>90%) under these reaction conditions The use of an aldehyde as co reductant in the reaction could be viewed as a drawback, but the corresponding carboxylic acid that is produced during the reaction may also be of interest and it is easily separated from the product epoxide We were also able to show that even nickel salts such as nickel(II) acetate, nickel(II) propionate and nickel(II) benzoate are also excellent epoxidation catalysts in the presence of oxygen and an appropriate aldehyde These nickel salts are not as soluble in organic solvents as are the nickel(II) β-diketonate complexes, but fortunately, only a small amount of catalyst (typically 1 mole % with respect to the alkene) is necessary for an efficient catalytic reaction In Chapter 1 of this thesis we mentioned the importance of an improved synthetic process for the production of carvone from limonene Using the nickel catalysts described in this thesis in conjunction with molecular oxygen and an aldehyde to convert limonene to its corresponding epoxide, could be the first step in a new route to carvone preparation as suggested in the following reaction scheme



Turning the above reaction scheme into a viable industrial process is one of the goals of a new IOP-Catalysis project that will be a continuation of some of the work described in this thesis Compound **4** in this scheme may act as a co-reductant for the nickel catalyzed converstion of **1** to **2**, making the use of an additional aldehyde unnecessary At the same time, **4** is converted into carvone, **5**

Summary

Epoxides are important intermediates in industrial and synthetic chemistry They have been traditionally prepared by a number of different methods beginning with the halohydrin method for industrial scale preparation On a laboratory scale, most epoxides are prepared from alkenes using a peroxy acid such as m-chloroperoxybenzoic acid as oxidant The potentially explosive nature of this reagent precludes the use of peroxy acids as oxidants on an industrial scale In recent years it has become of interest to develop industrial scale methods for the epoxidation of alkenes using molecular oxygen as oxidant under mild conditions From an industrial standpoint, molecular oxygen is an ideal oxidant because of its ready availability, low cost, and environmentally-compatible properties

In this thesis we describe two different approaches for the development of catalyst systems for the epoxidation of alkenes by molecular oxygen The first approach makes use of a manganese(III) porphyrin / Rh(III)bipyCp*Cl / formate catalyst couple for the reductive activation of molecular oxygen and the subsequent epoxidation of alkenes The first application of this system was in a two phase reaction mixture using aqueous and organic solvents as media The two-phase system was employed as a means of separating the manganese(III) porphyrin catalyst from the Rh(III)bipyCp*Cl / formate components which are the source of electrons The reductive activation of molecular oxygen is a two electron process In natural enzyme systems such as cytochrome P-450, these two electrons are supplied by NAD(P)H The exquisite control rendered by the enzyme system which delivers only two electrons to the metal-porphyrin per catalytic cycle is difficult to reproduce in the laboratory, but it is the most critical step in the reductive activation of dioxygen, the end result being the putative Mn(V)=O species that is responsible for oxygen transfer to the alkene substrate to form an epoxide In the two phase system, the Rh(III)bipyCp*Cl / formate couple was able to efficiently reduce Mn(III)TPP to Mn(II)TPP which is the first step in the activation of molecular oxygen We discovered that water soluble imidazoles, such as *N*-methyl imidazole, which are required as axial ligans to stabilize the Mn(V)=O complex from Mn(II)TPP and molecular oxygen, inhibited the reduction of Mn(III)TPP to Mn(II)TPP by blocking the formation of the Rh(III)-hydride species that must form in order for the reduction of Mn(III)TPP to occur *N*-Methylimidazole was able to bind to the free site on the rhodium that must be bound by formate ion *N* Methylimidazole, which was added to the reaction mixture to act as an axial ligand for the Mn(III)TPP, was therefore replaced by *N* decylimidazole a long chain imidazole that is only soluble in organic media Catalyst turnovers of 42 and 30 were obtained for *cis* stilbene and α-pinene, respectively We were not able to improve these turnover numbers because the Mn(III)TPP catalyst was degraded during the course of the reaction Even more robust porphyrins were not stable A possible agent that was responsible for the rapid degradation of the porphyrin catalsyts is a rhodium superoxo species that arises from the result of the reduced rhodium complex reacting with oxygen

To facilitate electron transfer from the reduced rhodium complex to the manganese(III) porphyrin catalyst, and thus prevent the formation of the rhodium-superoxo species, we designed a different catalyst system in which the manganese(III) porphyrin and Rh(III)bipyCp*Cl groups are joined together *via* a π-conjugated bridge, and a quinone containing π-conjugated spacer Both of these complexes were able to give epoxide yields approximately 10-fold higher in the presence of sodium formate than were found in the two-phase system Furthermore, the complexes were more stable than the Mn(III)TPP of the two-phase system For unknown reason, however, the reaction stopped after approximately 300 turnovers (with limonene as substrate)

The second approach for the epoxidation of alkenes with molecular oxgyen involved the use of nickel(II) β-diketonate and nickel(II) oxamide type complexes as catalysts in the presence of a co-reductant such as an aldehyde The scope of the reaction using nickel(II) β-diketonate catalysts was determined, and it was found that triply substituted alkenes such as α-pinene and limonene gave high yields of epoxides with bis-(3-*p*-*t*-butylbenzyl-2,4-pentanediono)-nickel(II) as catalyst in the presence of isobutyraldehyde Only branched aldehydes such as isobutyraldehyde and pivaldehyde were active as co-reductants under these conditions while straight-chain aldehydes or conjugated or aromatic aldehydes were inactive The selectivity for epoxide was high (>90%) and the reaction could be carried out either at 1 0 atmosphere oxygen pressure or in air without loss of selectivity Chiral nickel(II) β-diketonate derivatives, based on simple molecules from the chiral pool including camphor, menthone, and carvone did not give an enantioselective excess in the epoxidation of prochiral alkenes such as *trans*-stilbene and *trans*-β-methylstyrene

Investigations into the mechanism of the epoxide reaction catalyzed by nickel(II) β-diketonate complexes in the presence of molecular oxygen and isobutyraldehyde led us to propose that the active oxidizing species formed during the reaction is a cyclic metallo-peroxo complex that is formed as a result of the aldehyde binding to the nickel to give first the corresponding acyl radical and then the peroxo radical which is stabilized by the metal atom of the catalyst

In addition to nickel(II) β-diketonate complexes, nickel(II) oxamide type complexes are excellent catalysts for the epoxidation of alkenes by molecular oxygen in the presence of an aldehyde Like the nickel(II) β-diketonate complexes, the nickel(II) oxamide complexes are stable under the reaction conditions as long as there is enough substrate available for conversion to epoxide Triply substituted alkenes gave the highest epoxide yields Chiral nickel(II) complexes based on the oxamide macrocycle were prepared, but did not give enantiomeric excesses when used to epoxidize prochiral alkenes such as *cis*- and *trans*-β-methylstyrene Although the macrocyclic structure of the chiral ligand affords the necessary rigidity for the catalyst to induce an asymmetric transition state during the oxygen transfer step, the proposed radical nature of this process would prohibit the production of one enantiomer over the other

Finally, nickel(II) and manganese(III) salen complexes were modified with a molecular clip containing a binding site in an attempt to achieve substrate selectivity of dihydroxybenzene substrates that bind preferentially in the cavity of the catalyst While

the cavity-containing manganese(III) and nickel(II) complexes were able to catalyze the epoxidation of unfunctionalized alkenes in the presence of iodosylbenzene (Mn) and NaOCl (Mn and Ni) and in the presence of O_2/aldehyde (Ni), they were not able to bind dihydroxybenzenes in the cavity due to blockage of the binding sites by the methoxy groups on the walls of the clips. A binuclear nickel(II) salen complex modified with crown-ether groups was prepared to avoid this problem, but the complex could not be isolated in pure form from the reaction products for use in epoxidation reactions.

Samenvatting

Epoxiden zijn belangrijke verbindingen die worden gebruikt in de industrie en in het laboratorium. Zij kunnen op verschillende manieren worden bereid met de halohydrine methode als een van de eerste industrieel toegangelijke processen. Op een kleinere schaal, zoals in het laboratorium, worden epoxiden meestal gesynthetiseerd uit alkenen met behulp van een perzuur, b.v.*meta*-chloorperbenzoezuur als oxidant. Het explosieve karakter van perzuren maakt dat deze reagentia meestal ongeschikt zijn voor gebruik op een grotere (industriele) schaal. In de laatste jaren is er een groeiende belangstelling voor de ontwikkeling van industriele processen voor de epoxidatie van alkenen met behulp van moleculaire zuurstof die onder milde reactiecondities verlopen. Moleculaire zuurstof is vanuit industrieel oogpunt gezien een ideaal oxidatiemiddel vanwege het feit dat het goedkoop, gemakkelijk beschikbaar en milieuvriendelijk is.

In dit proefschrift zijn twee verschillende benaderingen voor de ontwikkeling van katalytische epoxidatieprocessen met behulp van moleculaire zuurstof beschreven. In de eerste benadering wordt gebruik van gemaakt van een katalysatorsysteem bestaande uit Mn(III) porfyrine / Rh(III) bipyridine / formiaat dat moleculaire zuurstof kan aktiveren en vervolgens alkenen kan laten epoxideren. Dit systeem werd eerst getest onder twee-fase-condities (water/organische oplossing), waarbij de katalysator (Mn(III)TPP) en de bron van elektronen (Rh(III)bipyCp*Cl/formiaat) van elkaar gescheiden zijn. Dit laatste is nodig omdat de reductieve activering van moleculaire zuurstof een twee-elektron proces is en een overmaat aan elektronen leidt tot verstoring van dit proces. In een enzymsysteem, zoals cytochroom P-450, zijn de twee elektronen afkomstig van NAD(P)H. De regulerende werking van het enzymsysteem, waarbij slechts twee elektronen overgedragen worden aan het metaal-porfyrine tijdens de reactiecyclus, is moeilijk na te bootsen met synthetische systemen, maar deze reductie is de cruciale stap in de reactie die leidt tot het ontstaan van het Mn(V)=O deeltje dat verantwoordelijk is voor de zuurstofoverdracht naar het alkeen.

In het twee-fase-systeem kon het Rh(III)bipyCp*Cl/formiaat op efficiente wijze het Mn(III)TPP tot Mn(II)TPP reduceren, zoals werd waargenomen met UV-vis spectroscopie. Er werd gevonden dat water-oplosbare imidazolen, die noodzakelijk zijn als axiale ligande voor het mangaanporfyrine, de reductie van Mn(III)TPP kunnen blokkeren door te binden aan het rhodiumcomplex Als het Rh(III)-hydride niet gevormd kan worden, wordt het Mn(III)TPP niet gereduceerd. Een niet in water oplosbaar imidazool zoals *N*-cetylimidazool blokkeerde de reductie van Mn(III)TPP niet. Met het twee-fase-systeem zijn turnovers van 42 en 30 behaald voor respectievelijk *cis*-stilbeen en α-pineen Hogere turnovers waren niet mogelijk vanwege de instabiliteit van de Mn(III)TPP katalysator onder deze reactiecondities. Een mogelijke reden voor de snelle

ontleding van de katalysator zou het ontstaan van een rhodium-superoxo deeltje kunnen zijn dat in staat is om het Mn(III)TPP molecuul af te breken

Om de overdracht van elektronen van het rhodiumcomplex naar het mangaancomplex sneller te laten verlopen is een systeem ontworpen waarbij het Mn(III)porfyrine en de Rh(III)bipyridine groepen aan elkaar gebonden zijn via een π-geconjugeerde brug of een spacer die een chinon groep bevat Deze met elkaar verbonden complexen zijn in staat om alkenen te epoxideren met een 10-voudige verbetering in turnover numbers in vergelijking met het eerder genoemd twee-fase systeem De reactie bleek te stoppen na ongeveer 300 turnover numbers De reden hiervoor is nog niet duidelijk, maar het blijkt ongunstig te zijn dat de reductie- en de oxidatiestap beide in een homogene oplossing plaatsvinden

Bij de tweede benadering voor de ontwikkeling van een katalytisch proces voor de epoxidatie van alkenen met moleculaire zuurstof is gebruik gemaakt van nikkel(II)β-diketonaat- en nikkel(II)oxamide-complexen als katalysatoren in aanwezigheid van zuurstof en een aldehyde als co-reagens De scope van de reactie is bepaald en er werd gevonden dat 3 voudige gesubstitueerd alkenen zoals α-pineen en limoneen hoge opbrengsten aan epoxide geven, met nikkel(II)β diketonaat-complexen als katalysator en isobutyraldehyde als co-katalysator Slechts vertakte aldehydes zoals isobutyraldehyde en pivaldehyde waren onder deze omstandigheden actief, terwijl onvertakte aldehydes of geconjugeerde en aromatische aldehydes inactief waren De selectiviteit voor epoxide was hoog (>90%) en de reactie kon uitgevoerd worden zowel bij 1 atmosfeer zuurstofdruk, als aan de lucht, zonder dat dit invloed had op de selectiviteit Chirale nikkel(II)β diketonaat verbindingen afgeleid van kamfer, menthon en carvon waren niet in staat de vorming van optisch actieve epoxides uit prochirale alkenen zoals *trans*-stilbeen en *trans* β-methylstyreen te katalyseren

Uitgebreide studies naar het mechanisme van de epoxidatiereactie gekatalyseerd door Ni(II)β-diketonaat-complexen in aanwezigheid van moleculaire zuurstof en isobutyraldehyde hebben tot de conclusie geleid dat het actieve oxiderende deeltje tijdens de reactie een cyclisch metaal-peroxo complex is, dat wordt gevormd na de binding van het aldehyde aan het nikkel Het gebonden aldehyde geeft eerst een acylradicaal en daarna een peroxo radicaal, dat gestabiliseerd wordt door het metaalcentrum

Naast de Ni(II)β-diketonaat-complexen blijken ook nikkel(II)oxamidecomplexen uitstekende katalysatoren te zijn voor de epoxidatie van alkenen met moleculaire zuurstof en een aldehyde Evenals de Ni(II)β diketonaatcomplexen, zijn de Ni(II)oxamide-complexen stabiel onder de reactie-omstandigeheden, zolang als er genoeg substraat beschikbaar is om omgezet te worden in het epoxide Drievoudig gesubstitueerde alkenen geven de hoogste opbrengst aan epoxide Chirale nikkel(II)complexen afgeleid van oxamide liganden gaven geen enantiomere overmaat te zien in de epoxidatie van prochirale alkenen zoals *cis*- en *trans* -β-methylstyreen Hoewel de macrocyclische

structuur van het chirale ligand de noodzakelijke starheid bezit om gedurende de zuurstofoverdracht een asymmetrische inductie te geven, verhindert het vermoedelijk radicale karakter van dit proces de preferente vorming van één van de twee enantiomeren.

In het laatste deel van het onderzoek zijn nikkel(II)- en mangaan(III)salencomplexen gesynthetiseerd die een substraat-bindingsplaats bezitten met als doel het bereiken van substraat-selectiviteit bij de reactie. Hoewel de holte-bevattende Mn(III)- en Ni(II)complexen in staat waren de epoxidatie van de niet-gefunctionaliseerde alkenen met behulp van iodosylbenzeen (Mn), NaOCl (Mn, Ni), en de combinatie aldehyde/O_2 (Ni) te katalyseren, bleken ze geen selectieve oxidatiereacties te geven, dit vanwege het feit dat hun bindingsplaatsen geblokkeerd worden door methoxygroepen die in het complex aanwezig zijn. Om dit probleem te vermijden, werd een binucleair nikkel(II)salencomplex gesynthetiseerd dat gemodificeerd is met kroonethergroepen. Dit complex kon echter niet in zuivere vorm geïsoleerd worden.

Curriculum Vitae

De schrijfster van dit proefschrift werd op 14 juni 1963 geboren te Stamford, Connecticut, U.S.A. In juni 1981 behaalde zij het high school diploma aan de New Canaan High School te New Canaan, Connecticut. In hetzelfde jaar werd begonnen met de studie aan de Northwestern Universiteit te Evanston, Illinois. Het graad van Bachelor of Arts werd in juni 1985 verkregen met als hoofdvakken Biochemie en Engels. Van juli 1986 tot augustus 1989 was de schrijfster werkzaam als onderzoeker op de afdeling Biologie van de Stanford Universiteit en van september 1989 tot juli 1990 als graduate student op de afdeling Chemie en Biochemie van de University of California, te Santa Cruz. Van januari 1991 tot april 1995 was de schrijfster verbonden aan de vakgroep Organische Chemie van de Katholieke Universiteit Nijmegen, waar onder leiding van Prof. Dr. R.J.M. Nolte, het in dit proefschrift beschreven onderzoek werd uitgevoerd De financiering van dit onderzoek vond plaats in het kader van het IOP-katalyse progamma van het Ministerie van Economische Zaken.